FORMULATION AND EVALUATION OF LURASIDONE BILAYER TABLETS

Dissertation Submitted in partial fulfillment of the requirement for the award of the degree of

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CHENNAI.

DEPARTMENT OF PHARMACEUTICS

K.M.COLLEGE OF PHARMACY

UTHANGUDI, MADURAI-625 107

APRIL - 2015

CERTIFICATE

This is to certify that the dissertation entitiled "**FORMULATION AND EVALUTION OF LURASIDONE BILAYER TABLETS "** submitted by **Mrs. R.RAMYA** in partial fulfillment of the degree of "**Master of Pharmacy** in **Pharmaceutics"** under the Tamilnadu Dr.M.G.R. Medical University, Chennai, done at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by her under my guidance and supervision during the academic year of **April 2014-2015**.This dissertation partially or fully has not been submitted for any degree or diploma of this university.

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R.Ramya

DEDICATED TO MY MOTHER , FATHER , HUSBAND, GURU AND BELOVED SON

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INTRODUCTION

An ideal dosage form regimen in drug therapy of my disease is the one which immediately attains the desired therapeutic concentrations of drug in plasma and maintain it constant for entire duration of treatment.

The drug may administered by variety of routes of dosage forms. The oral route of drug administration is most popular and has been successfully used for conventional delivery of drugs. It offers the advantage of convenience, ease of administration, greater flexibility in dosage forms design, ease of production and low cost. Hence it is adopted wherever possible. It is propable that at least 90% of all drug is used to produce systemic effects are administered by oral route.

The dosage forms available for oral administration are liquid like solution, suspension, emulsion and solids like powders, tablets and capsules. The physical state of most of the drug being solid which are administered in solid dosage forms.

Among the drugs that are administered orally, solid dosage form represents the Predefined class of product. They are versatile, flexible in dosage strength relatively stable, present lesser problem in formulation and packing and it is convenient to manufacture , store, handle and use. Solid dosage form provides best protection to the drug against temperature, humidity, oxygen, light and stress during transportation of two solid dosage forms that is tablets and capsules. The tablets are in wide use.[1,2]

1.1 TABLETS:[3,4]

Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents and prepared by either direct compression or moulding methods.

Advantages of tablets:[5]

- Ease of accurate dosing and low content variability
- Good physical and chemical stability

- Competitive unit production costs
- High level of patient acceptability
- High convenience
- Easy to package and ship
- Simple to identify
- Convenience of self administration.

Disadvantages of tablets:[5]

- Irritant effects on the gastro intestinal mucosa by some solids (e.g. aspirin)
- Possibility of bioavailability problems resulting from slow disintegration and dissolution
- Difficulty in swallowing in some patients; pediatrics and geriatrics
- Some drugs resist compression into tablets
- In emergency cases, intravenous or intramuscular injections are more effective.

Types of tablets:[6]

A) Oral Tablets for Ingestion

- Standard compressed tablets
- Multiple compressed tablets
    a. Layered tablets
    b. Compression coated tablets
    c. Inlay tablets
- Modified release tablets
- Delayed action tablets
- Targeted tablets
    a. Floating tablets
    b. Colon targeted tablets
- Chewable tablets

B) Tablets Used In the Oral Cavity

- Buccal tablets
- Sublingual tablets

- Troches and lozenges
- Dental cones

C) Tablets Administered By Other Routes

- Implantation tablets
- Vaginal tablets

D) Tablets Used To Prepare Solution

- Effervescent tablets
- Dispersible tablets
- Hypodermic tablets
- Tablet triturates

1.2 METHODS OF MANUFACTURING:[3]

Tablets are manufactured by either dry/ wet granulation or direct compression method.

Wet granulation:

It is the process in which a liquid is added to a powder in a vessel equipped with any of agitation that will provide agglomeration or granules. These granules are then compressed to form tablets.

Dry granulation:

In this technique no use of liquids. The process involves the formulation of slug. Then the slugs are mixed and screened to produce granules. These granules are then compressed to form tablets.

Direct compression:

The term direct compression is used to define the process by which the tablets are compressed directly, forms powder blends of active ingredients and suitable excipients [fillers, disintegrants and lubricants] which will flow uniformly in the die cavity and forms a firm compact.

Advantages of Direct compression:

- More economical.
- Less processing time and process validation.
- No need of moisture, heat and high compaction pressure.
- Optimization of tablet disintegration eg.starch more effective.

1.3 SUSTAINED RELEASE CONCEPT:

- The goals of sustained drug delivery are to conserve and maintain effective drug concentration, eliminate night time dosage, improve compliance and decrease side effects thus optimizing drug therapy.[7] Sustained release dosage forms provide a dosing of the drug from the product by supplying an initial amount (or) loading dose, perhaps one-half of the total dose release, followed by a gradual and uniform release of the remainder drug over the desired time period.
- Sustained release dosage form are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[8]

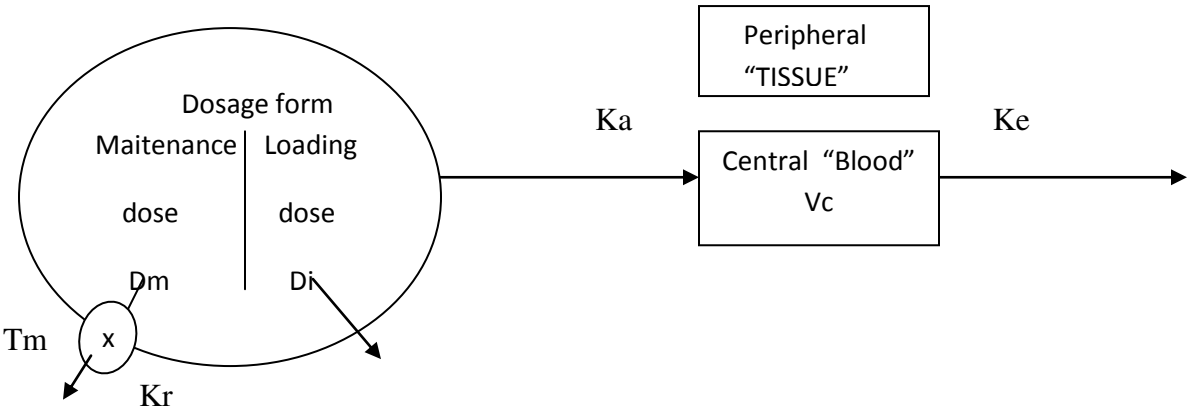
Advantages of Sustained Release Drug Delivery:[9]

- Reduced frequency of drug.
- Improved patient compliance
- Reduced blood level oscillation characteristic of multiple dosing of conventional dosage forms.
- Reduced amount of drug administration.
- Maximizing availability with a minimum dose.
- Safety margin of high potency drugs can be increased.
- Incidence of both local and systemic adverse effects can be reduced.
- Increased reliability of therapy.

Disadvantages of Sustained Release Drug Delivery:

- Administration of sustained release medication does not prompt termination of therapy.
- The physician has less flexibility in adjusting dosage regimen.
- Sustained release forms are designed for the normal population.
- Economic factors must also be assessed.

Pharmacokinetic Model of Sustained Release Dosage Form:



For optimizing sustained release dosage form designs, some specific parameters must be taken. These are:

- The loading or immediately available portion of the dose (Di).
- The maintenance or slowly available portion of the dose (Dm).
- The time at which release of maintenance dose begins (Tm).
- Specific rate of release (Kr) of the maintenance dose.

1.4 BILAYER TABLETS:

Bilayer tablets concept has long been utilized to develop extended release and immediate formulation for a single drug or combination of drugs [10]. Bi-layer extended release tablet generally has a fast releasing layer and control releasing layer to sustain the drug release. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration and the blood level is maintained at steady state by the sustained release layer [11]. The present study is planned to evaluate the suitability of different polymers for bilayer matrix tablets. Formulations were evaluated with respect to various parameters like weight variation, hardness, friability, thickness, content uniformity and *in -vitro* dissolution rate.

The immediate release layer and extended release layer were prepared by wet granulation technique. Hydroxypropylmethyl cellulose (HPMC 15 cps, HPMC 100 cps and Methocel K4MCR) was used as release rate retardant. Hydroxypropylmethyl cellulose (HPMC) is used frequently as a rate-controlling polymer in matrix tablets [12]. HPMC offers the advantages of

being non-toxic and relatively inexpensive; it can be compressed directly into matrices and is available in different chemical substitution and hydration rates and viscosity grades [13-14].

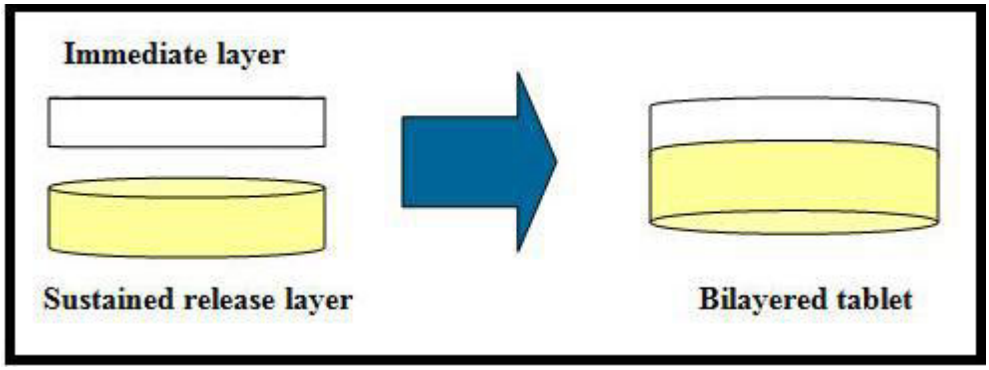


Fig.1.Bilayered tablets (same drug with different release pattern-homogenous)

NEED OF BILAYER TABLETS: [15,16,17]

1. For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive deliver systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s).
3. To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
4. To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).

IDEAL CHARACTERSTICS OF BILAYER TABLETS:

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
2. It should have sufficient strength to with stand mechanical shock during its production packaging, shipping and dispensing.

3. It should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

PREPARATION OF BILAYER TABLETS:[18,19,20,21]

Bilayer tablets to produce adequate tablet formulation, certain requirements such as sufficient mechanical strength desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression:

It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation:

It is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). The compression force on first layer was found to be major factor influencing tablet delamination.

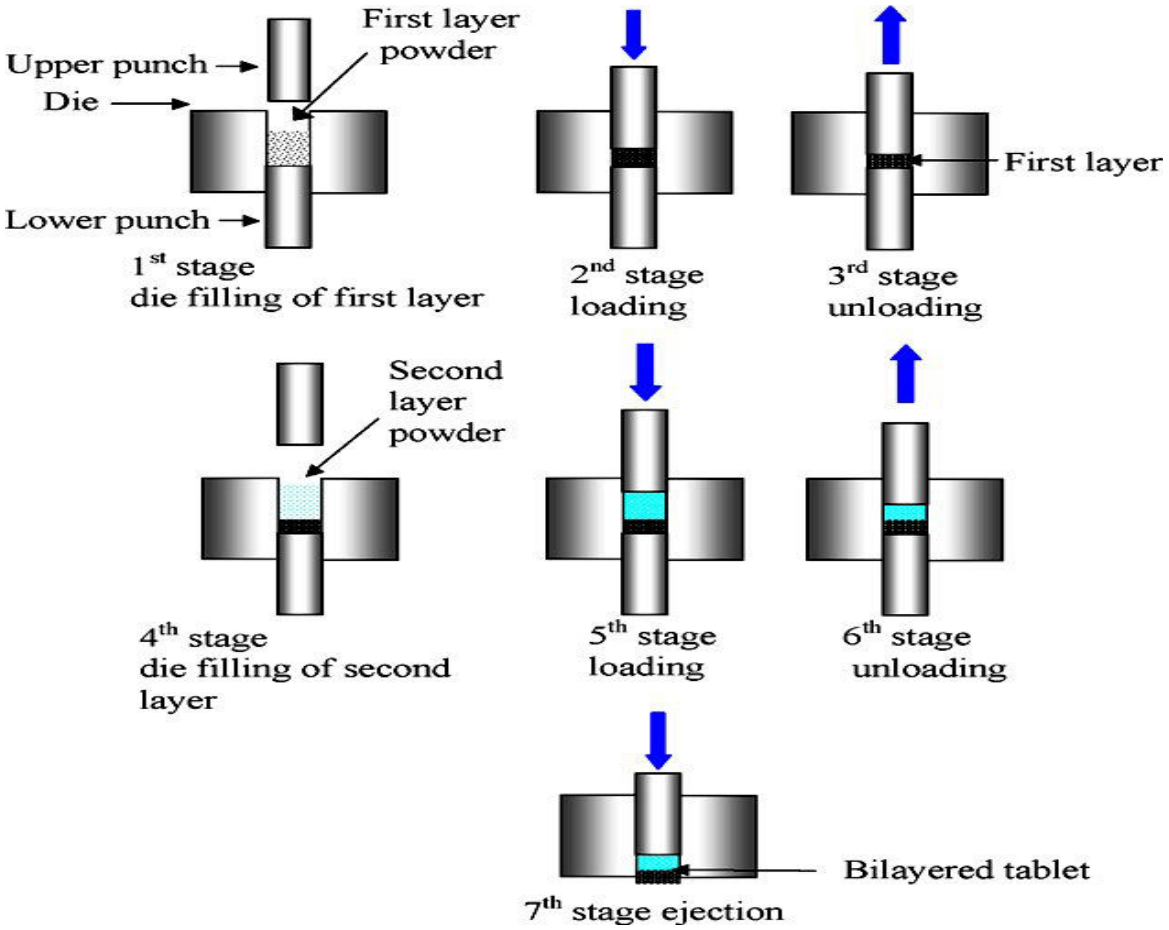


Fig 2: Preparation of bilayer tablet Compaction.

VARIOUS TECHNIQUES FOR BILAYER TABLET:

OROS® PUSH PULL TECHNOLOGY:[22,23,24]

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

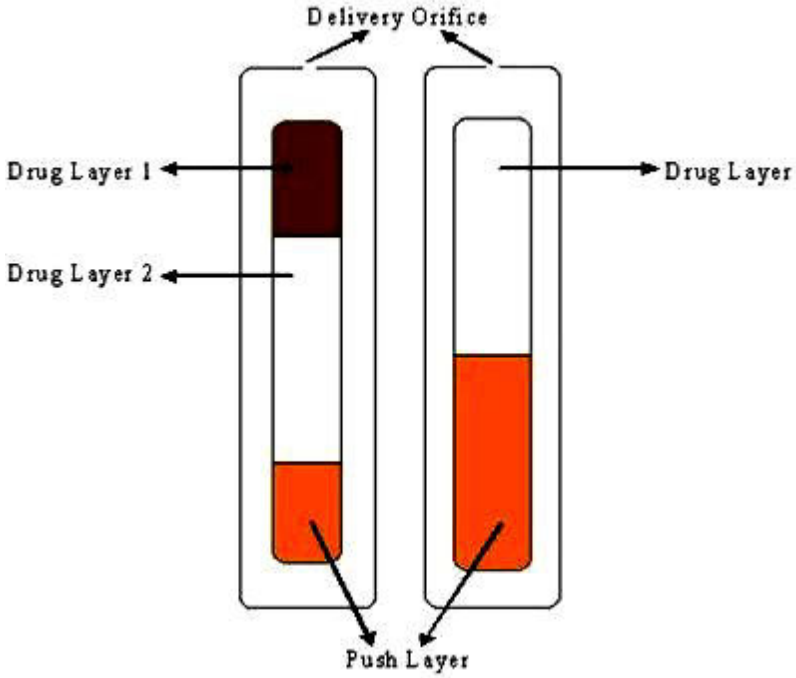


Fig. 3: Bilayer and trilayer OROS push pull technology

EN SO TROL TECHNOLOGY:

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

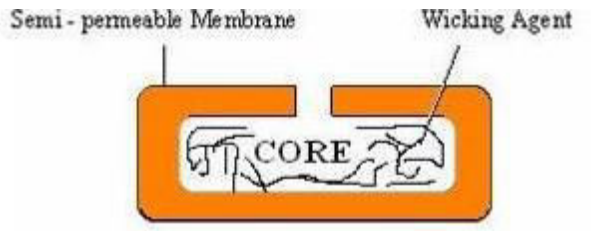


Fig: 4: EN SO TROL Technology

DUROS TECHNOLOGY:

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is

the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year.

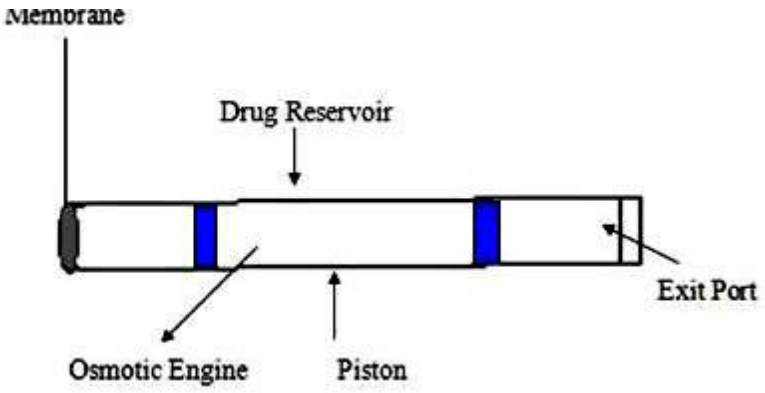


Fig. 5: DUROS Technology

ELAN DRUG TECHNOLOGIES DUAL RELEASE DRUG DELIVERY SYSTEM:

(DUREDAS Technology) is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tabletting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

BENEFITS OFFERED BY DUREDAS TM TECHNOLOGY INCLUDE:

- Bilayer tabletting technology.
- Tailored release rate of two drug components.
- Capability of two different CR formulations combined.
- Capability for immediate release and modified release components in one tablet.

L OROS TM TECHNOLOGY[22,23,24]:

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice.

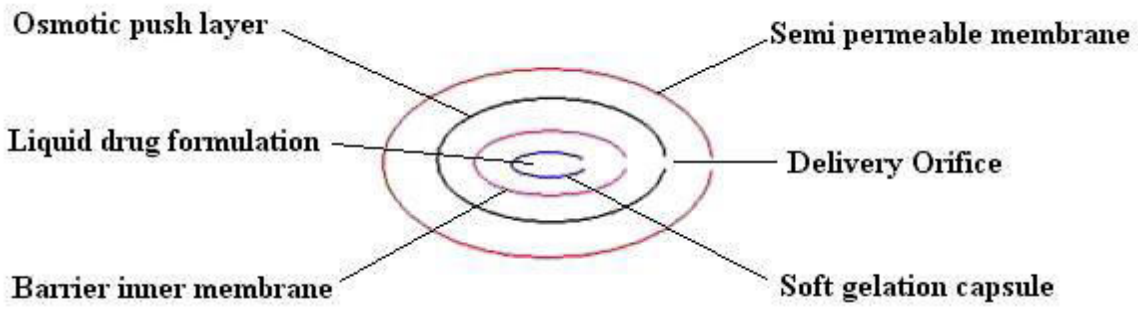


Fig.6: L–OROS TM Technology

SMALL-SCALE BI-LAYER

- 5 KN First Layer Tamping Force.
- 40 KN Precompression Force.
- 80 KN Main Compression Force.
- Single-Layer Conversion Capability

Advantages of the bi-layer tablet dosage forms are[25]:

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for thegreatest dose precision and the least content variability.
2. Cost is lower compared to all other oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Objectionable odour and bitter taste can be masked by coating technique.
7. Suitable for large scale production.
8. Greatest chemical and microbial stability over all oral dosage form.
9. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bi-Layer Tablet Dosage Forms are[25]:

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.

CHALLENGES IN BILAYER TABLETS MANUFACTURING[26]:

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.

Delamination:

Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross-contamination:

When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

Production yields:

To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

Cost:

Bilayer tableting is more expensive than singlelayer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development oftwo compatible granulations is must, which means more time spent on formulation development, analysis and validation.

2. LITERATURE REVIEW

Swati Aggarwal. et al.,[27] reviewed on the oral drug delivery system, types of tablets, and challenges in bilayer tablet manufacturing, various tablet presses used, quality and GMP requirements for their production and recent developments in the field of bilayer technology. Oral drug delivery remains the preferred route of drug delivery. Novel technologies with improved performance, patient compliance and enhanced quality have emerged in the recent past. Multilayer tableting is getting increasing attention from a variety of industries for a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. While general tablet manufacturing principles remain the same, there is much more to consider because making multi-layer tablets involves multiple-often incompatible products, additional equipment and many formulation and operation challenges.

Gattani SG. et al.,[28] developed a bilayer tablet of metoclopramide hydrochloride (MTH) and diclofenac sodium (DS) in separate layers to avoid incompatibility and thus to maximize the efficacy of both drugs in combination for the effective treatment of migraine headaches. MTH and DS were formulated as immediate and sustained release layers respectively. *In-vitro* dissolution kinetic studies of an optimized formulation of DS in both sustained release layer and bilayer tablet forms show good linearity of regression coefficient 0.9773 (first order equation). An optimized immediate release layer of MTH and a sustained release layer of DS might be suitable for the treatment of migraine by sequential release of the two drugs in a bilayer tablet.

Chithirra Anbalaghan. et al.,[29] prepared frusemide bilayer tablets. It consists of loading layer and controlled release layer. Crospovidone and sodium dodecyl sulphate were used for loading dose. Eudragit RL100 was used for controlled release layer. Tablets were evaluated for physicochemical properties such as hardness, friability, thickness, weight variation and drug content uniformity. FTIR studies revealed that there was no interaction between drug and polymers used in the study. *In-vitro* dissolution studies were carried out in USP type II paddle type apparatus. An Optimized formulation releases the drug up to 24 hours and it also fulfilled requirements such as easy to fabricate, inexpensive and high patient compliance.

Hosna Banu. et al.,[30] designed acetaminophen extended release bi layer tablets containing immediate release layer and extended release layer. Tablets were prepared by wet granulation technique using different grades of hydroxypropylmethyl cellulose as release rate retardant. *In- vitro* release rate decreased with increase of polymer loading and viscosity. Drug release was analyzed using zero-order, first order, Higuchi and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the bi layer matrix tablets. Mathematical analysis of the release kinetics indicated that release from the matrix tablets followed Fickian diffusion. So the bi-layer tablets could be a potential dosage form for delivering acetaminophen.

Jain Jitendra. et al.,[31] developed a bilayer-floating tablet (BFT) for Indomethacin using direct compression technology were punched using optimized solid dispersion, HPMC K4M, Avicel PH-112, ac-di-sol, magnesium stearate and aerosil in fast release layer and optimized floating layer as sustained release layer. Tablets were evaluated for physico-Chemical properties such as Hardness, Friability, Thickness, weight Variation and drug content uniformity. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. *In- Vitro* dissolution studies were carried out in a USP type II Paddle type apparatus. The optimized formulation showed no significant changes on stability studies when storing at 4º c, 40º c, /75%RH, 60ºc /80% RH for 3 months. Optimized formulation release the drug up to 24hrs and fulfilled many requirements such as easy to fabricate, cost effective and high patient compliance.

Reddi Prashanth. et al.,[32] worked on bilayer tablets containing Losartan Potassium for immediate release using sodium starch glycolate as super disintegrant and Metoprolol succinate for extended release using Carbopol 71G, Hydroxy Propyl Methyl Cellulose (HPMC K100M), Xanthan gum and poly ethylene oxide as hydrophilic polymers and Kollidone as binder. The immediate layer was prepared by direct compression and extended release layer by wet granulation method. The tablets were evaluated for physiochemical properties. All the values were found to be satisfactory and were within limits with low standard deviation. *In-vitro* release studies were carried out using USP type II paddle apparatus in phosphate buffer (pH

6.8) for 12 h as dissolution medium. The best formulation was subjected accelerated stability studies and the formulation retained its physic chemical characteristics even after stressed **.**

Antony Loebe. et al.,[33] was designed to evaluate the short-term efficacy and safety of once-daily lurasidone (80 mg/day and 160 mg/day) in the treatment of an acute exacerbation of schizophrenia.

Crewe, Cheshire. et al.,[34] sugessted Lurasidone is a novel benzoisothiazol antipsychotic that has recently been approved for the treatment of schizophrenia in the U.S. Like many other second-generation antipsychotics, it has a high affinity fordopamine D(2) and serotonin 5-HT(2A) receptors as well as a high affinity for 5-HT(7) receptors. It has negligible affinity for α(1) adrenoceptors, histamine H(1) receptors or muscarinic acetylcholine M(1) receptors. It has demonstrated efficacy in short-term trials versus placebo. The incidence of extrapyramidal symptoms (excluding akathisia/restlessness) was greater with lurasidone (14.7%) than placebo (5.1%). Akathisia and somnolence were dose-related adverse events. Lurasidone appears to have relatively little effect on weight, plasma glucose or lipids to date. No evidence of QTc prolongation was seen and orthostatic hypotension was uncommon. Raisedprolactin levels in short-term studies were dose-dependent, greater in females and occurred overall in 3.7 and 0.7% of lurasidone and placebo recipients, respectively.

Nirav K. Joshi.et al.,[35] developed and validated for the estimation of Lurasidone Hydrochloride in the Pharmaceutical dosage form. UV Spectrophotometric method was a simple one by estimation of Drug at 230 nm over the concentration range 10-50 ìg/ml for Lurasidone. The % recovery of the drug was found to be 98.5% – 100.16 %. Linearity was obtained 0.996 in the concentration range of 10-50 ìg/ml for Lurasidone. LOQ and LOD were found to be 8.43 and 2.81 µg/ml respectively at 230nm for Lurasidone Hydrochloride. Assay of The Lurasidone Hydrochloride in Pharmaceutical Dosage Form was found to be 99.3 ± 1.44 %. Methods were validated according to ICH guidelines and can be used for analysis of dosage form.

Kirson NY. et al.,[36] evaluated the effect of study designed on the comparative effectiveness of antipsychotic formulations. The optimal use of different antipsychotic formulations in a general clinical setting depends on better understanding of the underlying reasons for differences in effectiveness across research designs. While long-acting (depot) antipsychotic medications are often recommended to address adherence problems, evidence on the comparative effectiveness of depot versus oral antipsychotics is inconsistent.

Herbert Y. Meltzer. et al.,[37] designed to evaluate the short-term efficacy and safety of lurasidone in the treatment of acute schizophrenia. Lurasidone is a recently approved antipsychotic drug for schizophrenia, with daily doses up to 80 mg. Doses above that level were associated with increased levels of akathisia in this 6-week study. At recommended doses, lurasidone is efficacious for both positive and negative symptoms with no effect on metabolic parameters. Olanzapine was associated with greater significant improvement on some measures but also had increased metabolic effects.

Jonathan M Meyer. et al.,[38] described the development of lurasidone, including its receptor binding affinities, pharmacokinetics, CNS activity in rodent models and results of early clinical efficacy and safety studies in humans. Lurasidone has a high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors as well as for receptors implicated in enhancement of cognitive function (e.g., 5-HT_7, 5-HT_{1A}, α_{2c}). Lurasidone has no affinity for muscarinic M_1 and histamine H_1 receptors and minimal affinity for α_1 adrenoceptors, dopamine D_1 and D_3 receptors, serotonin 5-HT_{2C} receptors and α_{2A} adrenoceptors. Phase II efficacy data indicate that lurasidone doses from 40 to 120 mg/day are effective in the treatment of schizophrenia, with positive symptom reduction exceeding that for negative symptoms, as seen with other antipsychotics. Preclinical data indicate that lurasidone reverses MK-801 induced learning and memory impairment in rodents, and active comparator data from a Phase Ib study of lurasidone 120 mg/day versus ziprasidone 160 mg/day also found a signal for effects on cognition. Phase II studies suggest that lurasidone has no significant QTc prolongation and a benign metabolic profile**.**

New York University School of Medicine. et al.,[39] worked for the treatment of acute schizophrenia in adults, and asenapine is also approved for the maintenance treatment of schizophrenia and as a monotherapy or as an adjunct to lithium or valproate for the treatment of bipolar manic or mixed episodes. The expectation is that these new agents will be less problematic regarding treatment-emergent weight gain and metabolic disturbances, which unfortunately can occur with several other second-generation antipsychotics. Asenapine is a sublingual preparation, in contrast to iloperidone and lurasidone, which are swallowed. Iloperidone and asenapine are dosed twice daily, in contrast to lurasidone, which is dosed once daily with food. Both asenapine and lurasidone can be initiated at a dose that is possibly therapeutic, but iloperidone requires 4 days of titration to reach its recommended target dose range. Although both asenapine and lurasidone can be associated with dose-related treatment-emergent akathisia, iloperidone is essentially free of extrapyramidal adverse effects or akathisia throughout its recommended dose range. Sedation and/or somnolence have been reported with each medication. They are the most common adverse events associated with asenapine treatment, and are clearly dose-related for lurasidone. In contrast, no therapeutic dose response for iloperidone, asenapine, or lurasidone is clearly evident from short-term clinical trials. Longer-term and naturalistic studies will be helpful in evaluating these agents and their role in the psychiatric armamentarium.

Henry A. Nasrallah. et al.,[40] evaluated the efficacy, safety, and tolerability of treatment with the atypical antipsychotic lurasidone for patients with an acute exacerbation of schizophrenia. Patients were randomized to 6 weeks of double-blind treatment with lurasidone and placebo. Changes in Positive and Negative Syndrome Scale (PANSS) scores were evaluated using mixed-model repeated-measures (MMRM) analysis. Vital signs, laboratory parameters, extrapyramidal symptoms, and electrocardiogram were assessed. In this study, in which a large placebo response was observed, lurasidone was statistically superior to placebo in treating acute exacerbation of chronic schizophrenia. All lurasidone doses were generally well tolerated.

Amol Chaudhary. et al.,[41] developed once-daily extended release tablet of Lamotrigine, were prepared by the wet granulation method. Lamotrigine using hydrophilic matrix material (Methocel K4M & Methocel K100LV) in combination with hydrophobic material (Eudragit L-30D-55) were used, which can release the drug upto 24hrs in predetermined rate. Diluents used were lactose monohydrate and magnesium stearate as lubricant. The formulated tablets were also characterized by physical and chemical parameters. The granules showed satisfactory flow properties, compressibility, and drug content. The *in-vitro* release rate profile showed the higher concentration of 04-50ERT polymer in tablet, the combination of hydrophilic in core and hydrophobic in coating polymer showed less result than use of a single polymer.

Ravisankar P. et al.,[42] developed and validated for the determination of Lurasidone HCl in bulk and pharmaceutical formulations. Beer's law is obeyed in the concentration range of 2-10µg/mL with good correlation coefficient (R2= 0.9995) and UV detection was done at 315 nm. The percentage recovery studies were performed and the percentage recovery was found to be of 98.76 -99.84 %. The method was precise and the relative standard deviation was found to be 0.98. Detection limit and Quantitation limit were found to be 0.253 µg/mL and 0.766 µg/mL respectively. The proposed method was successfully validated as per the ICH guidelines. This method can be used for the determination Lurasidone HCl in quality control laboratories without interference of excipients.

Glen Oaks. et al.,[43] designed Lurasidone is a new second-generation (atypical) antipsychotic approved for the treatment ofschizophrenia in adults. The recommended dose is 40-80 mg given once daily, with no titration needed. Lurasidone should be taken with food. The tolerability profile of lurasidone is noteworthy in terms of a good weight and metabolic profile and no cardiovascular adverse effects such as orthostatic hypotension or prolongation of the QTc interval. Lurasidone is associated with some somnolence,akathisia, nausea, and parkinsonism, especially early in treatment. It might be helpful for cognitive or depressive symptoms; early findings have shown some benefit in these areas, but additional studies are needed. Lurasidone may be particularly helpful for patients with schizophrenia who are overweight or have endocrine problems (diabetes, dyslipidemia) or comorbid cardiovascular conditions

M. Nischala. et al.,[44] reviewed an introduction to bi-layer tablet technology, challenges in bi-layer tablet manufacturing, various tablet presses used, quality and GMP requirements for their production various techniques used for bi-layer tabletting and recent developments in the field of bi-layer technology. A controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. General tablet manufacturing principles remain the same, there is much more to consider because making multi-layer tablets involves multiple often incompatible products, additional equipment and many formulation and operation challenges.

Gurpreet Arora. et al.,[45] developed an oral controlled release mucoadhesive matrix tablets of domperidone using natural mucoadhesive material myrrh oleo gum resin (MOGR). The tablets were formulated with the natural polymer in different concentration (5, 10, 15 and 20 % w/w) employing direct compression technology. The tensile strength increases from 0.973±0.09 to 1.687±0.11 MN/m2 and mucoadhesive strength from19.868 to 49.778 N with the increase in natural polymer concentration from 5 to 20 % (M1 to M4). Swelling index of natural polymer was testified towards proliferation by together increasing gum concentration and the time period. Accelerated stability studies demonstrate no significant change in the tensile strength, mucoadhesive strength and drug assay.

Arun Kumar Das. et al.,[46] developed a stable formulation of antipsychotics Quetiapine as an immediate-release tablet. Quetiapine has beneficial calming properties and successfully treats the symptoms of aggression, anxiety and hostility that can accompany acute exacerbations

of schizophrenia. The task of developing immediate release tablet is accomplished by using a suitable diluent and super-disintegrants. Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in less time. The optimized formulation is further selected and compared with the release profile of the innovator product and similarity factor was conducted. The result was found to be more than 50%.The optimized formulation was conducted for stability studies according to ICH guideline. There were insignificant changes during studies. Hence, the results suggest the feasibility of developing immediate release tablets consisting of Quetiapine, which has an excellent tolerability profile offering high patient acceptability that may promote patient adherence to medication and an improved quality of life.

Morsu Ashok. et al.,[47] developed controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is better than the traditionally used mouthwash,sprays,gels So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bi-layer tablet is suitable for sequential drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Several pharmaceutical companies are currently developing bilayer tablet for a variety of reason: patent extension, therapeutic, marketing to name a few. To reduce capital investment quite often existing but modified tablet presses are used to develop such tablets. The present article provides an introduction to bilayer tablet technology, advantages and disadvantages, various techniques, quality and GMP requirements, characterization and evaluation of bilayer tablets. Bilayer tablet, various techniques, bilayer tablet presses, GMP requirements characterization and evaluation of bilayer tablet.

Motarwar S.S. et al.,[48] developed to reduce capital investment quite often existing but modified tablet presses are used . Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer

tablet is improved beneficial technology to overcome short coming of single layer tablet. In the last decade interest in developing a combination of two or more active pharmaceutical ingredient in a single dosage form(bilayer tablet)has increased in the pharmaceutical industry, promoting patient convenience and compliance. several pharmaceutical companies are currently developing bilayer tablet for a variety of reason: patentextension, therapeutic, marketing to name a few.

Arvind Mishra. et al.,[49] developed bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. Using a modified tablet press may therefore not be your best approach in producing a quality bi-layer tablet under GMP-conditions, especially when high production output is required. Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system.

Preeti Karwa. et al.,[50] designed in bilayer tablet of Zolpidem Tartrate for biphasic release and *in- vitro* evaluation of the same. Bilayer tablets comprised two layers, i.e. immediate release and controlled release layer. The immediate release layer comprised croscarmellose sodium as a super disintegrant and the controlled release layer comprised HPMC K100M as the release retarding polymers. Direct compression method was used for formulation of the bilayer tablets. HPMC K100M extended the release of drug from the extended release layer for 6 hr. There were no changes observed in physicochemical properties and drug release pattern of tablets. Biphasic drug release pattern was successfully achieved through the formulation of bilayer tablets in this study.

Jaldhara S Patel.et al.,[51] developed controlled release formulation along with various features to provide a way of successful drug delivery system. Controlled release dosage forms have been extensively used to improve therapy with several important drugs. Use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bi-layer tablet is suitable for

sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet.

Rohan D. Deshpande. et al.,[52] developed to achieve controlled delivery of different drugs with pre-defined release profiles. A combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). The development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be your best approach to producing a quality bi-layer tablet under GMP-conditions. Especially when in addition high production output is required.

Buchi N. Nalluri. et al.,[53] formulated controlled release (CR) oral matrix tablet formulations of Carvedilol (CAR), an antihypertensive using cellulose ether polymer, Hydroxy Propyl Methyl Cellulose (HPMC K4M, HPMC K15M) of different viscosity grades as drug release retardants. The tablets were prepared by direct compression technique and evaluated for various physico-chemical/mechanical parameters. Based on the viscosity and gel formation during dissolution, HPMC K4M was selected as release retardant. Based on the dissolution data obtained with different fillers and keeping in view of the results from the pre-compression studies, and gel layer retaining with the matrix tablets, Avicel PH 105 was selected to carry out further formulation development. The formulation containing 25%w/w HPMC K4M as release retardant and Avicel PH 105 gave 96.59 ± 3.1% release at the end of 24h and fulfils regulatory requirement.

V.Hima Bindu. et al.,[54] designed on controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose.

Pruthvipathy R. Katikaneni. et al.,[55] designed Pseudoephedrine hydrochloride sustained release tablets to prepare direct compression with ethylcellulose (EC). Initially, different viscosity grades of EC were studied. An increase in viscosity grade resulted in a marginal to moderate increase in the release rate. However, lower viscosity grades produced harder tablets. The highly compressible 10 cp grade was used to study the effect of drug loading, particle size, compression force, and magnesium stearate concentration on release properties. The rate of drug release decreased with a decrease in the drug concentration in the matrix. The square of the release rate is proportional to drug concentration in the matrix, indicating that the release of pseudoephedrine hydrochloride from EC matrices is primarily matrix-controlled.

Shankar S. J.et al.,[56] prepared Modified release matrix tablets of ciprofloxacin hydrochloride with different polymers. The powder mixture was compressed by direct compression method into tablets using rotary tablet compression machine equipped with 13mm tooling of convex surface. Prepared tablets were evaluated for uniformity of content, hardness, thickness, weight variation, friability, *in-vitro* dissolution studies and stability studies. The *in-vitro* dissolution study was carried out using USP dissolution test apparatus (paddle type) at100 rpm. The test was carried out at 37 ± 0.5 ^{0}C in 900ml of the N/10 Hcl buffer as the medium for two hours, and pH 7.2 buffer from 2nd hour to 12th hour. The average weight of tablet was observed to be within limits. *In-vitro* dissolution study indicated that matrices containing Chitosan and Guar gum in the ratio 2:1 showed 93.6 % release after 12 hrs. Whereas for the matrices containing lactose in the percentage of 50 and 75 showed 96.15 % and 99.90 % release after 12 hrs respectively. The prepared matrix tablets have not undergone any change either in

physical appearance, content or in the dissolution pattern after storage at 45° C & 75 % RH over a period of 6 months.

Hamdy Abdelkader. et al.,[57] developed Baclofen from matrix tablets prepared by a hot-melt granulation process (wax tablets) and wet granulation process (E-RS100 and E-L100 tablets). Statistically significant differences were found among the drug release profile from different classes of polymeric matrices. Higher polymeric content (40%) in the matrix decreased the release rate of drug because of increased tortuosity and decreased porosity. At lower polymeric level (20%), the rate and extent of drug release was elevated. The release kinetics was found to be governed by the type and content of the excipients (polymer or filler). The prepared tablets showed no significant change in drug release rate when stored at ambient room conditions for 6 months.

Leslie Citrome. et al.,[58] developed Lurasidone is a second-generation antipsychotic newly approved by the U.S. Food and Drug Administration for the treatment of schizophrenia. Similar to most other second-generation antipsychotics, lurasidone is a full antagonist at dopamine D2 and serotonin 5HT2A receptors. Efficacy within the dose range of 40–120 mg/d was established in four 6-week, randomized, controlled trials. The recommended starting dose is 40 mg/d and the maximum recommended dose is 80 mg/d. Doses above 80 mg/d do not appear to confer added benefit and may be associated with a dose-related increase in certain adverse reactions such as somnolence and akathisia. Lurasidone is primarily metabolized in the liver through the CYP3A4 enzyme system, and coadministration with drugs that are strong inhibitors of CYP3A4 (such as ketoconazole) or strong inducers (such as rifampin) are contraindicated. Lurasidone is associated with minimal weight gain and no clinically meaningful alterations in glucose, lipids, or the ECG QT interval.

Mali Nikita. et al.,[59] developed for the estimation of Lurasidone hydrochloride in bulk and pharmaceutical formulations. Lurasidone hydrochloride was estimated at 227 nm in UV-spectroscopic method (Method A), 237 nm in first order derivative spectroscopy (Method B) and scanned at 225.0 - 235.0 nm in Area under Curve method (Method C). Linearity range was found

to be 5-30 µg/ml (Correlation coefficient r = 0.999in method A, r = 0.999 in method B and r = 0.999 in method C) in all the three methods. These methods were tested and validated for various parameters according to ICH guidelines. The proposed Methods were successfully applied for the determination of Lurasidone hydrochloride in pharmaceutical formulation (Tablets). The results of recovery were found to be 99.44-101.28 % for method A, -100.33- -101.46% for Method B, and for Method C % Recovery was found to be 99.83-100.76% which was within limits. (98-102%). Limit of Detection and Limit of Quantification were 0.2044, 0.6196 for method A, 0.6350, 1.9245 for method B and 0.0831, 0.2521 for method C. The results demonstrated that the procedure is accurate, precise and reproducible (% relative standard deviation <2%), while being simple, cheap and less time consuming and can be suitably applied for the estimation of Lurasidone hydrochloride in tablet dosage forms.

Muvvala S Sudhir. Et al.,[60] designed spectrophotometric method of analysis for lurasidone in bulk form was developed and validated. The absorbance was found to increase linearly with increasing concentration of lurasidone, which is corroborated by the calculated correlation coefficient value (r2 = 0.999). The linear regression analysis data for the calibration plot showed good linear relationship with in the concentration range of 10 – 60 µg/ml. The limit of detection and limit of quantitation were found to be 1.25316 µg/ ml and 3.797468 µg /ml respectively. This method was tested and validated for various parameters according to ICH guidelines. The results demonstrated that the procedure is accurate, precise and reproducible (R.S.D. < 2 %).

Xiao Huang. et al.,[61] reviewed experimental observations of burst release in monolithic polymer controlled drug delivery systems, theories of the physical mechanisms causing burst, some of the unique ideas used to prevent burst, and the treatment of burst release in controlled release models. The fast release of drug in a burst stage is utilized in certain drug administration strategies, the negative effects brought about by burst can be pharmacologically dangerous and economically inefficient. Therefore a thorough understanding of the burst effect in controlled release systems is undoubtedly necessary.

Koichiro Tahara. et al.,[62] designed sustained release (SR) from tablet matrices prepared with hydroxypropyl methylcellulose (HPMC) 2910 polymers were investigated to define the conditions for selection of appropriate polymers for SR formulation development. It is well known that the two important parameters for the release of drug from tablet matrices are the infiltration rate of medium into the matrix, for those drugs with reasonable aqueous solubility, and the erosion rate of the matrix system, for those drugs with poor aqueous solubility. In addition, the amount of drug loaded into the tablet also influences the release rate of the drug. The infiltration rate of medium into the matrix can be controlled by changes in the interspace volume of the matrix by the use of higher levels of materials such as lactose, which quickly rinse out of matrix system. The larger interspace volumes produced by the higher ratio result in more rapid release of the drug. The viscosity of HPMC polymers is related to the molecular weight and has a large influence on the erosion rate of matrix tablet. Use of a low viscous grade HPMC polymer is desirable for drugs that are poorly water soluble since the erosion rate of the tablet matrix is the controlling factor for drug release. The release rate of poorly soluble drug can be controlled by the rate of tablet erosion. The tablet erosion rate can also be adjusted by the choice of HPMC polymer viscosity or by mixing HPMC of different viscosity grades.

Mohammad Usman.et al.,[63] developed Mefenamic acid 200 mg controlled release matrices by direct compression and *in- vitro* drug dissolution studies were performed to find out the drug release rate and patterns. Methocel was used as rate controlling polymer. Also the effect of several co-excipients was investigated on the drug release rates during *in-vitro* dissolution studies. Polymer Methocel was used as a rate controlling polymer and was formulated with the drug at 4 different D: P ratios. Phosphate buffer pH 7.2 was used as dissolution medium using PharmaTest dissolution apparatus. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics. Dissolution equivalency evaluation was performed using f_2 similarity factor.

Mayank Bansal. **et al.,**[64] formulated an immediate release tablet of Zaltoprofen for the treatment of pain and inflammation, by using superdisintgrant such as Croscarmellose sodium and different grades of microcrystalline cellulose. Immediate release tablets of Zaltoprofen were

prepared by direct compression method using superdisintgrant such as Croscarmellose sodium and different grades of microcrystalline cellulose in different ratios. Sodium starch glycolate was added to aid disintegration. Tablets were subjected to physicochemical characterization such as thickness, hardness, friability, weight uniformity, drug content, disintegration time, *in-vitro* drug release, and stability study. Tablets were found to be satisfactory when evaluated for thickness, hardness, friability, weight uniformity, drug content, disintegration time and *in-vitro* drug release. The tablet disintegration time was less than one minute for all the tablet formulations. The *in-vitro* drug release in optimized formulation was found to be 98.89 % in 45 min. The optimized formulation also showed satisfactory hardness (5.83±0.556 kg/cm2), friability (0.425%±0.0029), drug content (98.29%±0.0657), weight variation (270.21±0.2184 mg), disintegration time (25.02±0.0028seconds) and stability.

3. RESEARCH ENVISAGED

3.1 AIM OF WORK

In the present work Lurasidone have been developed as a Bilayer Tablet formulation which is designed to get the Immediate Release and controlled release for 24 hours.

Psychosis is an abnormal condition of mind that causes people to perceive or interpret things differently from those around them.

Lurasidone is an atypical antipsychotic that is a D2 and 5-HT2A (mixed serotonin and dopamine activity) to improve cognition. It reduce the extra pyramidal side effects that are often associated with typical antipsychotics. It's half life is 18 hrs . Because of short half life and need of quick onset of action, Bilayered tablets were formulated.

Bilayer Tablet consist of two layers are

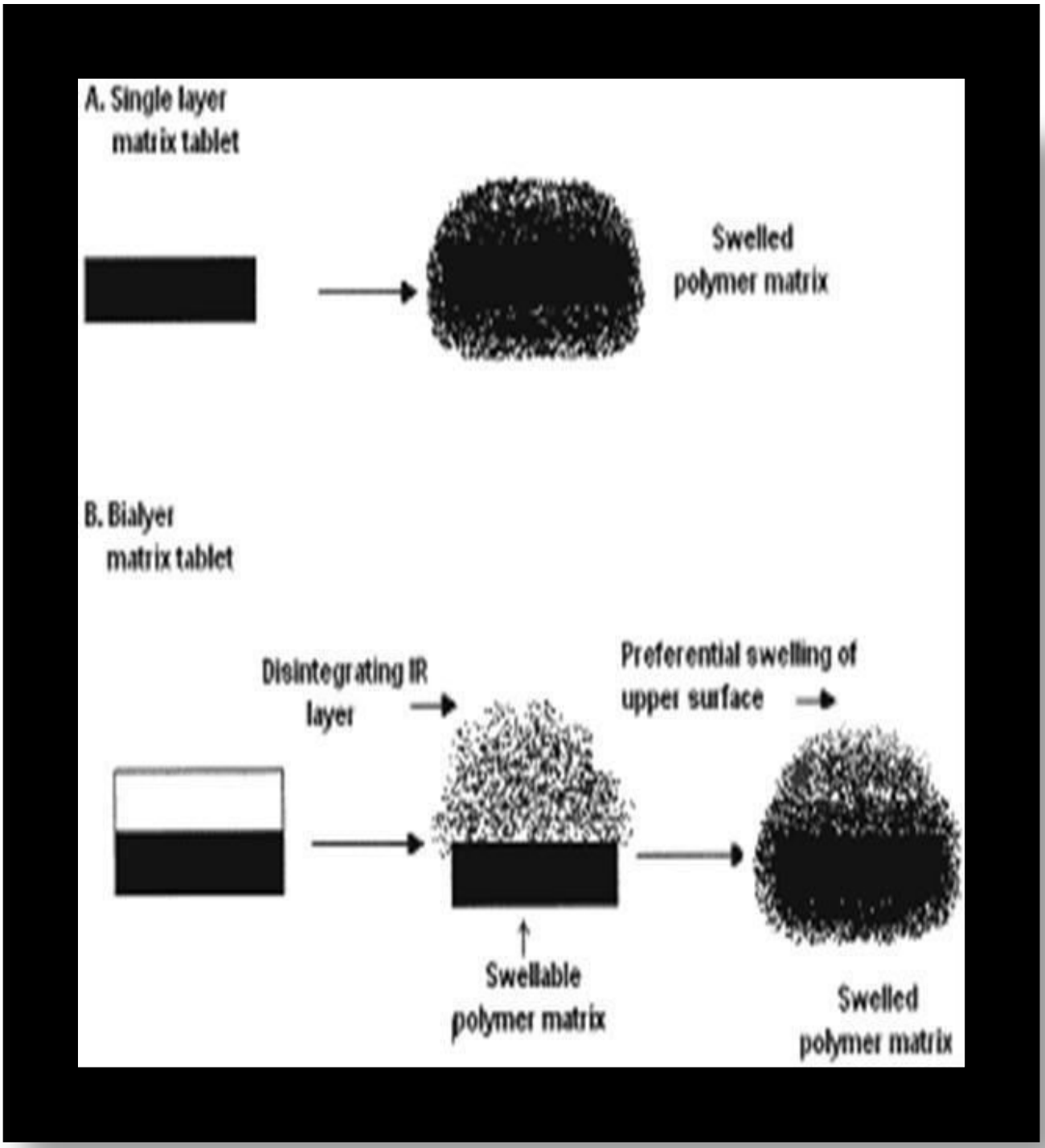
1. Immediate Release
2. Sustained Release

When this bilayer tablet swallowed first fast release layer will dissolve immediately and give the onset of action. The remaining sustained release layer gives the therapeutic activity slowly until 24^{th} hours.

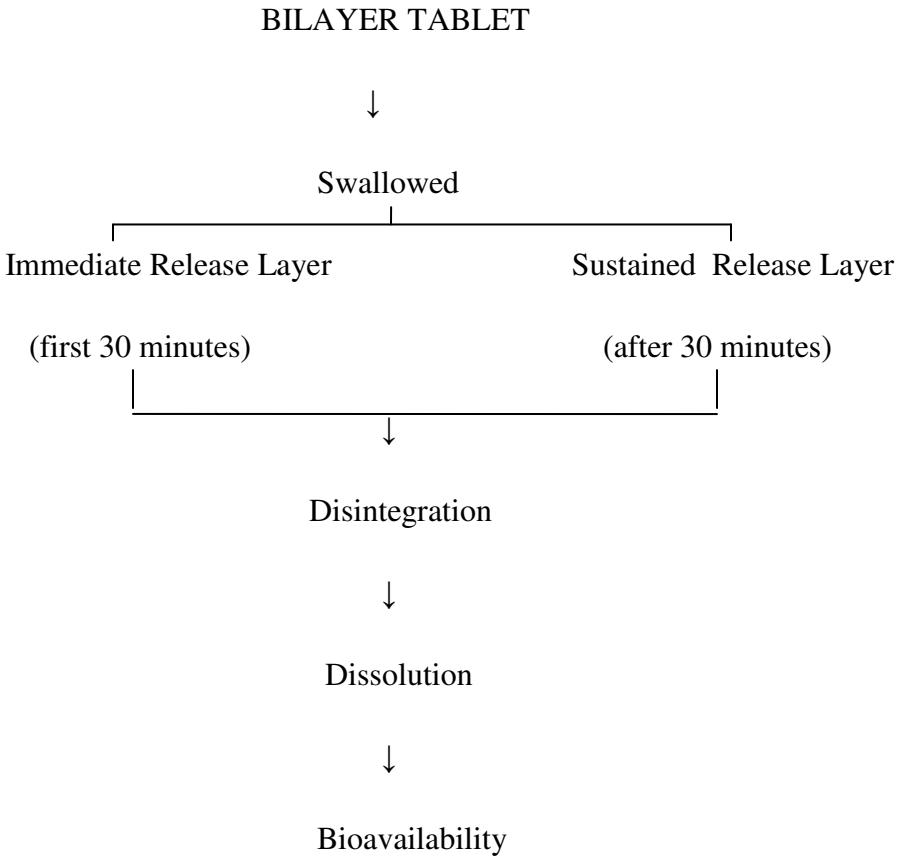
Objective of Lurasidone Tablet:

Lurasidone bilayer tablets were formulated with following objectives

- To get controlled release.
- To get quick onset of action.
- To get quick dissolution of drug.
- To get more bioavailability.
- To prevent dose dumping.
- To access patient compliance.
- To get dual action.


A. Single layer matrix tablet
Swelled polymer matrix
B. Bialyer matrix tablet
Disintegrating IR layer
Preferential swelling of upper surface
Swellable polymer matrix
Swelled polymer matrix

SCHEME FOR MECHANISM OF BILAYER TABLET



3.2 PLAN OF WORK

The scheme of the proposed work is as follows,

- Preformulation studies
    - Angle of Repose
    - Bulk Density
    - Tapped Density
    - Hausner Ratio
    - Carr's Index
- FTIR Studies
- Preparation of Lurasidone Bilayer Tablet by Direct compression
- Evaluation of Bilayer Tablet
    - Diameter
    - Hardness
    - Thickness
    - Friability
    - *Invitro*-Dissolution Study
- Stability studies
- Investigation of drug release kinetics

4. METHODOLOGY

4.1 MATERIALS USED:

S.NO	MATERIALS	SUPPLIERS
1	Lurasidone	Kekule Pharma Ltd, Hyderabad.
2	Crospovidone	Shasun Chemicals, Pondicherry.
3	Croscarmellose	Shasun Chemicals, Pondicherry
4	Hydroxy propyl methyl cellulose	Vigro chem, India.
5	Sodium lauryl sulphate	Global Remedies & Drug Pvt., Ltd, Hosur.
6	Micro crystalline cellulose	Himedia Labs, Mumbai.
7	Magnesium stearate	Siani Pharmaceticals, India
8	Talc	Udaipur Minerals, India
9	Starch	Udaipur Minerals, India

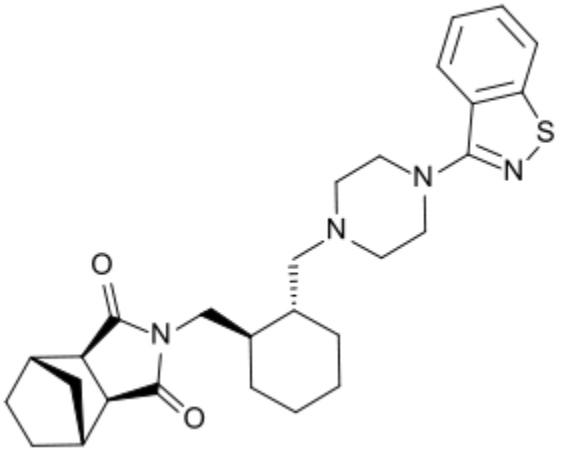
4.1.1 INSTRUMENTS USED:

S.NO	INSTRUMENTS	SUPPLIERS
1	Single pan electronic balance	Shimadzu corporation, Japan
2	pH meter	Elico Pvt Ltd, Chennai.
3	Dissolution apparatus	DISS 2000, Lab India, Chennai
4	Disintegration tester	Electolab, Chennai
5	Vernier calipers	Mitutoyo corps, Japan
6	Hardness tester	Monsanto, India
7	Single beam UV-Visible Spectrophotometer	Shimadzu corporation 1201, Japan
8	16 Station Rotary tablet compression machine	Cadmach, India
9	FTIR Spectrophotometer	Perkin-Elmer, Germany
10	Stability chamber	Osworld, Mumbai

4.1.2 DRUG PROFILE

LURASIDONE[42,65]

General Description:



Chemical Name:

(3a*R*,4S,7*R*,7aS)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl piperazin-1-ylmethyl]cyclohexylmethyl} hexahydro-4,7-methano-2*H*-isoindole-1, 3-dione hydrochloride

Molecular Formula:

C28H36N4O2S·HCl

Molecular Weight:

529.14

Description:

Lurasidone hydrochloride appears as a white to light yellow crystalline powder and stable upto thirty six months. sparingly soluble In chloroform and acetonitrile ; slightly soluble in ethanol; in water and acetone very slightly soluble in water and acetone , insoluble in toluene and 0.1 N HCl.

Melting Point:

198–205^{0}C

Density:

1.273 g/cc

Mechanism of action:[65]

Lurasidone is an atypical antipsychotic that is a D2 and 5-HT2A (mixed serotonin and dopamine activity) to improve cognition. It is thought that antagonism of serotonin receptors can improve negative symptoms of psychosis and reduce the extrapyramidal side effects that are often associated with typical antipsychotics.

Pharmacokinetics:[66]

Lurasidone is readily absorbed and quickly reaches maximal concentrations (Cmax) within 1-4 hours. When taken with food, there is a two-fold increase in exposure and time to maximal concentration is increased by 0.5-1.5 hours. This occurs regardless of fat or caloric content. Bioavailability = 9-19%.

Distribution:

Volume of distribution of Lurasidone is 613L and 99% Lurasidone bound to serum proteins.

Metabolism:

Lurasidone is metabolized in the liver via the enzyme CYP3A44. This means that its plasma concentrations may be increased when combined with CYP3A4 inhibitors like ketoconazole or grape fruit juice, possibly leading to more side effects.

Excretion: Lurasidone excrets mainly by feces (80%) and by urine (9%) also

Therapeutic Uses:[67]

Treatment of schizophrenia.

For treating the cognitive and memory deficits.

Contraindication:[68]

Elderly patients with dementia-related psychosis.

Placebo-treated patients.

Pregnancy and Breast-feeding.

Dosage and Administration :

For adults with schizophrenia, the recommended initial dose is lurasidone 40 mg orally daily with food. Initial dose titration is not required. The maximum recommended daily dose is 80 mg. In patients with moderate and severe renal impairment (creatinine clearance [CrCl], 10–50 ml/minute) and for those with moderate and severe hepatic impairment (Child–Pugh class B and C), the lurasidone dose should not exceed 40 mg/day. No dosage adjustments are necessary in the geriatric population.

4.1.3 Excipients Profile:[69,70]

1. CROSPOVIDONE (Kollidon CL)

Synonyms:

Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; PolyplasdoneXL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name :

1-Ethenyl-2-pyrrolidinone homopolymer.

Functional Category:

Tablet disintegrant

Description:

Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Typical Properties:

Acidity/alkalinity	:	pH = 5.0–8.0 (1% w/v aqueous slurry)
Density	:	1.22 g/cm3
Density (bulk)	:	0.35 g/cm3
Density (tapped)	:	0.45 g/cm3
Moisture content	:	Maximum moisture sorption is approximately 60%.
Solubility	:	Practically insoluble in water and most common organic solvents.
Specific surface area	:	1.0 m2/g
Storage Conditions	:	Crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Safety:

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

Applications:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by directcompression.

Crospovidone can be used to enhance the solubility of poorly soluble drugs in co-evaporation technique.

2. Croscarmellose sodium

Synonyms:

4C-Di-Sol, cross linked carboxy methyl cellulose sodium, modified cellulose gum nymulzsx, primellose, solutab.

Chemical Name:

Cellulose, carboxy methyl ether sodium salt, cross linked.

Moleculaer Weight:

90000-700000

Functional Category:

Tablet and capsule disintegrants.

Description:

Croscarmellose sodium occur odorless, white or grayish white powder.

Melting Point:

It browns at approximately 227^{o}C, chars at approximately 252^{o}C.

Stability and storage conditions:

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression with Croscarmellose sodium as a disintegrants, showed no significant difference in drug dissolution after storage at 30^{o}C for 14 months.

It should be stored in well closed container in a cool and dry place.

Safety:

It is regarded as a essential non-toxic and non-irritant materials.

Application:

Croscarmellose sodium is used in oral pharmaceutical formulation as a disintegrant for capsule, tablets and granules. In tablet formulation, Croscarmellose sodium is used in both direct compression and wet granulation process. Concentration of up to 5%w/w of Croscarmellose sodium is used as a tablet disintegrant although normally 2%w/w is used in tablets by direct compression.

3. Magnesium Stearate:

Synonyms:

Stearic acid, Magnesium salt, Magnesium octadeconate.

Functional Category:

Tablet and capsule lubricant.

Description:

It is fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and characteristic taste.

Typical Properties:

Density(tapped) : 0.286 g/cm^3

Density(bulk) : 0.159 g/cm^3

Solubility:

It is soluble in water, ethanol and ether, slightly soluble in warm benzene and warm ethanol.

Melting Point:

117-150^oC

Stability and Storage Conditions:

It should be stored in a well closed container in cool and dry place. It is a stable compound.

Incompatibilities:

Incompatible with strong oxidizing agent, strong acids, alkalies and iron salts. It cannot be used in product containing aspirin, some vitamins and most alkaloid salts.

Safety:

It is widely used in pharmaceutical formulation and is generally regarded as a non-toxic material. However oral consumption of large quantity may result in some laxative effect or mucosal irritation.

Application:

It is widely used in cosmetics, food and pharmaceutical formulation. It is used as lubricant in capsule and tablet formulation at 0.25-5% concentration.

4. Talc:

Synonyms:

Magsilomanthus, Magsil star, Purified chalk, Powderde talc.

Chemical Name:

Talc.

Functional Category:

Anticaking agent, Glidant, Diluent and Lubricant for tablet and capsule.

Typical Properties:

Hardness **:** 1-1.5

Specific Gravity **:** 2.7-2.8

Acidity / Alkalinity **:** 6.5-10

Hygroscopic **:** Absorbs more amount of water at 25^{o}C up to 90%

Solubility:

Insoluble in dilute acids and alkalis, organic solvents and water.

Stability and Storage Conditions:

Talc is a stable material. It may be sterilized by exposure to ethylene oxide and heating and heating at 160^{o}C. Talc should be stored in a well closed container in cool and dry place.

Safety:

Talc is mainly used in tablet and capsule formulation. Inhalation fo talc caused irritation and severe respiratory distress in infants. The ovarian cancer is increased in women when using talc to its carcinogenic potential.

Application:

Talc is widely used as a lubricant and diluents in oral solid dosage formulation. It is also used as dusting powder in topical preparation. It is also used as a lubricant in food products and cosmetics.

5. Sodium Lauryl Sulphate:

Synonyms:

Laurylsiran sondy , NaDS, Natrium laurylsulfuricum, SDS,SLS,Sodium lauril sulfate, sodiumdodecyl sulfate

Chemical formula :

$C_{12}H_{25}NaO_4S$

Molecular weight:

Monoisotopic-288.137124653

Description:

Sodium lauryl sulfate is an anionic surfactant naturally derived from coconut and / or palm kernel oil.it usually consisting of a mixture of sodium alkyl sulfates , mainly the lauryl.

Function Category:

Binder

Application :

SLS lowers surface tension of aqueous solution and is used as fat emulsifier , wetting agent and detergent is also in cosmetics , pharmaceuticals and toothpasters. It is also used in creams and pasters to properly disperse the ingredients and as research tool in protein biochemistry.SLS also has some microbial activity.

6. HYPROMELLOSE (HPMC K4M, K100M)

Synonyms:

Benecel MHPC; E464; Hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Chemical Name:

Cellulose hydroxypropyl methyl ether.

Functional Category:

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity increasing agent.

Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Typical Properties:

Acidity/alkalinity **:** pH = 5.5–8.0 for a 1% w/w aqueous solution.

Ash **:** 1.5–3.0%, depending upon the grade and viscosity.

Autoignition temperature**:** 360°C

Density (bulk) : 0.341 g/cm3

Density (tapped) : 0.557 g/cm3

Density (true) : 1.326 g/cm3

Melting point : Browns at 190–200°C; chars at 225–230°C.

Glass transition point : 170–180°C.

Moisture content : Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relativehumidity of the surrounding air.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity:

1.26

Viscosity (dynamic):

A wide range of viscosity types are commercially available.

Table 1: Typical viscosity values for 2% (w/v) aqueous solutions of HPMC. Viscosities measured at 20°C.

Methocel product	Nominal viscosity (mPas)
HPMC K4M	4,000
HPMC K100M	100,000

Stability and Storage Conditions:

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose

undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Safety:

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Applications:

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. It is also used as a suspending and thickening agent in topical formulations. It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. It is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

7. **CELLULOSE, MICROCRYSTALLINE (Avicel PH-101):**

Synonyms:

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres ; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name :

Cellulose

Functional Category :

Adsorbent; suspendin agent: tablet and capsule diluent; tablet disintegrant.

Description:

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties:

Density (bulk) **:** 0.32 g/cm for Avicel PH-101

Density (tapped) **:** 0.45 g/cm for Avicel PH-101

Density (true) **:** 1 .512–1.668 g/cm

Melting point : Chars at 260–270°C.

Moisture content : Typically less than 5% w/w. Microcrystalline cellulose is hygroscopic.

Particle size distribution: Typical mean particle size is 20–200 μm.

Solubility:

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Safety:

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential.

Applications:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in directcompression processes. It is also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 2: Uses of Microcrystalline cellulose.

Use Concentration (%)
Adsorbent 20–90
Antiadherent 5–20
Capsule binder/diluents 20–90
Tablet disintegrant 5–15
Tablet binder/diluents 20–90

8. STARCH:

Synonyms:

Amido; amidon; amilo; amylum; aytex p; cassava starch; fluftex W; melojel; paygel 55; pure-dent; tablet white.

Description:

It occurs as an odorless and tasteless, fine, white-colored powder comprised of very small spherical or ovoid granules whose size and shape are characteristics for each botanical variety.

Functional category:

Glidant; tablet and capsule diluents; tablet and capsule disintegrant; tablet binder.

Solubility:

Practically insoluble in cold ethanol 95% and cold water.

P^H:

5.5-6.5

Density:

Bulk - 0.462 gm/cm^3

Tapped- 0.658 gm/cm^3

Moisture content:

Hygroscopic and rapidly absorb atmospheric moisture.

Stability and storage condition:

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid dosage forms, starch is considered to be inert under normal storage conditions.

Incompatibilities:

Nil

Safety:

It is widely used as an excipient in pharmaceutical formulations, particularly oral tablets. It is an edible food substance and is generally regarded as an essentially non-toxic and non-irritant material.

Applications:

It is widely used as an excipient in oral dosage formulations where it is utilized as a binder diluent and disintegrant. In tablet formulations, freshly prepared starch paste is used at a concentration of 5-25% w/w in tablet granulations as a binder. It is one of the most commonly used tablet disintegrants at concentration of 3-15%w/w.

5. EXPERIMENTAL INVESTIGATION

5.1 CONSTRUCTION OF STANDARD CURVE OF LURASIDONE:[71]

a) By UV spectroscopy method:

Lurasidone was estimated spectrophotometrically at 230nm and it obeys beer-lamberts law in the range of 5 – 25 mcg/ml.

PROCEDURE:

1) PREPARATION OF MCIl VAINES BUFFER:

2.58 gm of 0.1M Citric acid was taken in 1000 ml standard flask (0.1M = 21 gm of Citric acid in 1000 ml distilled water) and 1.2 gm of 0.2M sodium di hydrogen phosphate (0.2 M = 156 gm of sodium di- hydrogen phosphate in 1000 ml distilled water) was taken and made up to 1000 ml with distilled water.

1. Preparation of Standard curve of Lurasidone pH 3.8 buffer::

a) Preparation of primary stock solution:

100 mg of lurasidone was taken in 100 ml standard flask. Then it was dissolved in 50 ml of methanol and made up to 100 ml volume with MCllVaines buffer to a concentration of 1000 mcg/ml.

b) Preparation of secondary stock solution:

From primary stock solution 5 ml was taken in 100 ml standard flask and made up to 100 ml volume with MCllVaines buffer to a concentration of 50 mcg/ml.

c) Sample solution:

From secondary stock solution aliquots ranging from 1 to 5 ml were pipette out and diluted to 10 ml with MCllVaines buffer to get the concentration of 5, 10, 15, 20, 25 mcg/ml the absorbance was measured at 230nm.

2. Standard curve of Lurasidone HCL in pH 7.4 buffer:

a) Preparation of primary stock solution:

100 mg of lurasidone was taken in 100 ml standard flask. Then it was made up to 100 ml with phosphate buffer pH 7.4 to a concentration of 1000 mcg / ml.

b) Preparation of secondary stock solution:

From primary stock solution 5 ml was taken in 100 ml standard flask and made up to 100 ml volume with phosphate buffer pH 7.4 to a concentration of 50 mcg/ml.

c) Sample solution:

From secondary stock solution aliquots ranging from 1 to 6 ml were pipette out and diluted to 10 ml with phosphate buffer pH 7.4 to get the concentration of 5, 10, 15, 20, 25 and 30 mcg/ml the absorbance was measured at 230nm.

A standard graph was plotted by keeping the known concentration on X axis and obtained absorbance on Y axis.

Table:3 Data for standard curve of Lurasidone pH 3.8 buffer::

Concentration (mcg / ml)	Absorbance
5	0.191
10	0.375
15	0.561
20	0.750
25	0.942

Fig:1 STANDARD CURVE OF LURASIDONE IN MCllVaines buffer:

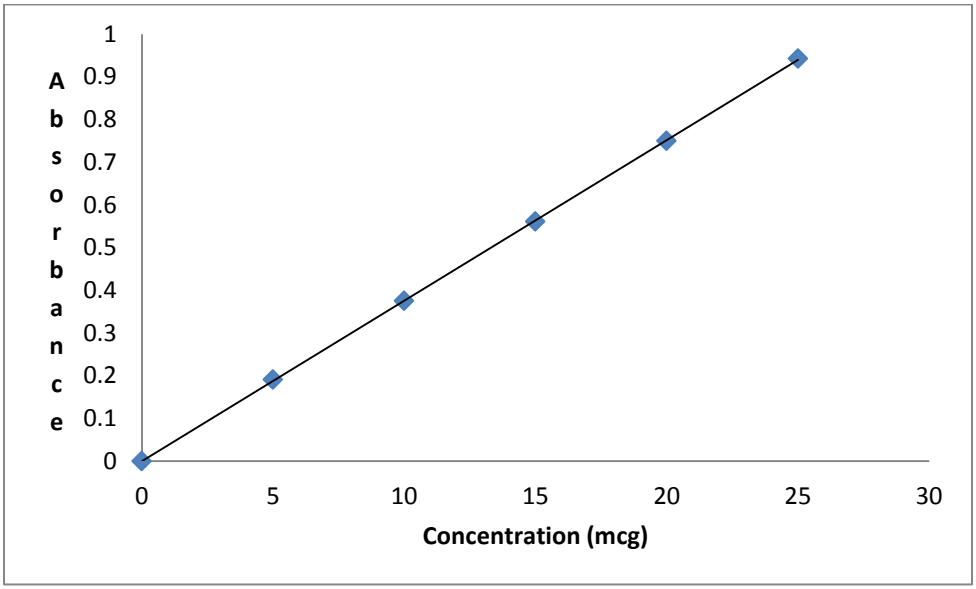
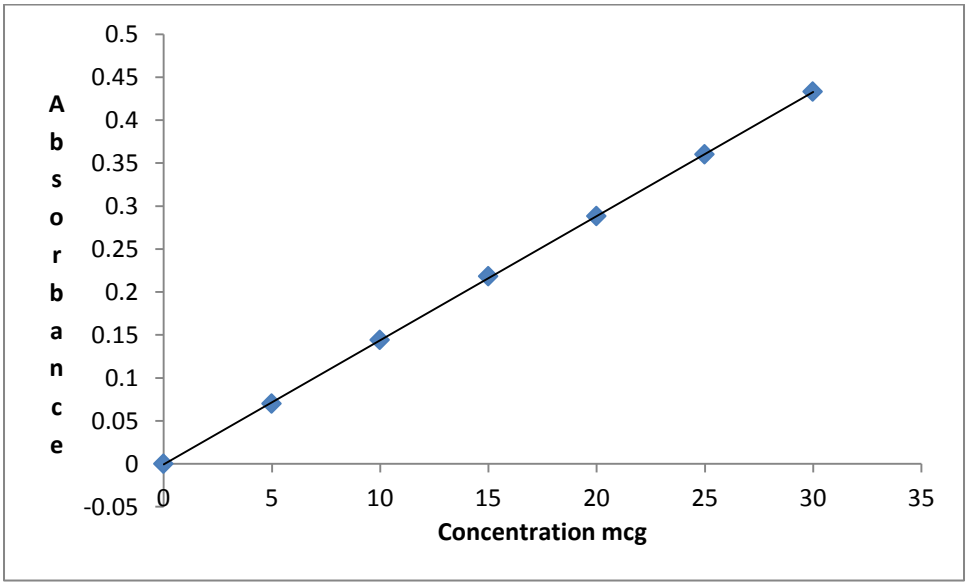


Table:4 Data for standard curve of Lurasidone pH 7.4 buffer::

Concentration (mcg / ml)	Absorbance
5	0.07
10	0.144
15	0.211
20	0.280
25	0.342
30	0.407

Fig:2 STANDARD CURVE OF LURASIDONE IN pH 7.4 buffer::



5.2 PREFORMULATION STUDIES:[72,73]

- Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms.
- The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.
- The use of preformulation parameters maximizes the changes in formulating an acceptable, safe, efficacious and stable product.
- The drug (Lurasidone) in powder form and granules were subjected to the following physical test for 3 times and average values were noted.

5.2.1 I.R SPECTRUM FOR LURASIDONE:

The IR spectrum of substances compared with that odtained concomitantly for the corresponding USP reference standard, provides perhaps the most conclusive evidence of the identity of the substance. Potassium bromide(KBr) method was carried out. Lurasidone and KBr were compressed under 15 tones pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 400 to 4000 cm^{-1} in IR spectrometer.

5.2.2 DRUG- EXCIPIENTS COMPATIBILITY STUDIES:

About 500 mg of Lurasidone alone and mixtures cosisting of Lurasidone with various excipients in 1 : 1 and 1 : 10 ratio in glass vial were taken and kept at various accelerated condition [25^{o}C / 60% RH, 30^{o}C / 75% RH, 40^{o}C / 75% RH] in stability chamber. It is carried for one month in open and closed glass vials. At the interval days of 1, 2, 3, 4, 5, 6, 14, 21 and 30 days samples were withdrawn and physical characteristics like colour were recorded. Finally the mixtures with no colour change were selected for formulations.

5.2.3 Determination of Angle of Repose:

The pure drug and granules were subjected to angle of repose by funnel method. The frictional forces in a loose powder can be measured by the angle of repose, Θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. The angle of repose is calculated by

$$\Theta = \tan^{-1}(h/r)$$

Θ = angle of repose

h = height of the conical heap

r = radius of the base of the heap

5.2.4 Determination of Bulk Density and Tapped Density:

An accurately weighed quantity of the powder (or) granules (W) were carefully poured into the graduated cylinder and the volume(V_0) was measured. The graduated cylinder was fixed in the density determination apparatus and tapped for 250 times and again subjected to 500 taps till the constant reading was obtained(V_f). The bulk and tap densities were calculated using the following formulae

Bulk density = W/ V_0

Tapped density = W/ V_f

W = weight of the powder

V_0 = initial volume

V_f = final volume

5.2.5 Determination of Hausner Ratio and Carr's Index:

Hausner ratio and carr's index are the measures of interparticle friction and the potential powder arch (or) bridge strength and stability respectively which have been widely used to estimate the flow properties of powder.

Hausner ratio and carr's index were calculated using the following equation:

$$\text{Hausner ratio} = \frac{\rho_{tap}}{\rho_{bulk}}$$

ρ_{tap} = tapped density of powder

ρ_{bulk} = bulk density of

$$\text{Carr's index} = \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} \times 100$$

5.2.6 Loss on Drying:

It was done in Electronic Loss on Drying (LOD) apparatus (Sartorius, Germany). Weighed quantity of 1 gm sample was placed in the pan and the temperature was increased to 105^{o}C and the loss on drying in % was noted.

5.3 FORMULATION OF BILAYER TABLETS

Preparation of immediate release layer of Lurasidone:

Lurasidone immediate release tablets were prepared by using direct compression method. Lurasidone, Croscarmellose sodium, Crospovidone powder, Sodium Lauryl Sulphate, and starch were accurately weighed and passed through sieve number 40. All the ingredients as shown in Table 4 were mixed in a polybag. Magnesium stearate and Talc were added after passing through sieve number 40 and mixed homogenously .

Table:5 COMPOSITION OF IMMEDIATE RELEASE LAYER OF LURASIDONE:

Ingredients	Category	F1 (mg)	F2 (mg)	F3 (mg)
Lurasidone	Active ingredient	12	12	12
Croscarmellose sodium	Superdisintegrant	10	-	10
Crospovidone	Superdisintegrant	-	10	10
Sodium lauryl sulphate	Surfactant	4	4	4
Magnesium stearate	Lubricant	1	1	1
Talc	Glidant	1	1	1
Starch	Diluent	172	172	162

Preparation of sustained release layer of Lurasidone:

Lurasidone sustained release tablets were prepared by using direct compression method. Lurasidone, Hydroxy Propyl Methyl Cellulose (HPMC), and Micro Crystalline Cellulose were accurately weighed and passed through sieve number 40.mixed homogenously. All the ingredients as shown in Table 5 were mixed in a polybag. Magnesium stearate and Talc were added after passing through sieve number 40 and mixed homogenously .

Table:6 COMPOSITION OF SUSTAINED RELEASE LAYER OF LURASIDONE :

Ingredients	Category	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Lurasidone	Active ingredient	28	28	28	28	28	28	28	28	28
HPC	Polymer	14	28	-	-	-	-	-	-	-
HPMC(K4)	Polymer	-	-	14	28	42	14	28	42	56
HPMC(K100)	Polymer	-	-	-	-	-	14	28	42	56
Magnesium stearate	Lubricant	4	4	4	4	4	4	4	4	4
Talc	Glidant	4	4	4	4	4	4	4	4	4
MCC	Diluent	400	386	400	386	372	386	358	330	302

*each tablet weight is 450mg

Tablet Compression:

The bilayer tablet compression was made using 10mm punch in a 16 station rotary tablet machine. In this, sustained release Lurasidone granules were introduced first into the die cavity and a slight pre-compression was made so that the layer was uniformly distributed after that immediate release Lurasidone granules were added and a final compression was made.

5.4 EVALUATION OF TABLETS:[74,75]

a) Thickness and Diameter:

The thickness and diameter of the tablets were carried out using vernier caliper (Mitutoyo corps, Japan). Five tablets were used for the above test from each batch and results were expressed in millimeter.

b) Hardness Test:

Tablets required a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, handling and shipping. The hardness of tablets were measured by "Monsanto hardness tester". Five tablets were used for hardness studies and results were expressed in Kg/cm^2

c)Weight variation Test:

Twenty tablets were selected at random individually weighed in a single pan electronic balance (Ax, shimadzu –corporation Japan) and the average weight was calculated. The uniformity of weight was determinied according to I.P specification. As per I.P not more than two of individual weight would deviate from average weight by more than 5% and non deviate more than twice that percentage.

d)Friability Test:

The friability of the tablets were determined by Roche friabilator. In this apparatus, the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of six inches with each revolution. Pre-weighed 20 tablets were placed in f riabilator, which is then operated for 100 revolutions. The tablets were then dusted and re-weighed. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable.

$$\text{Friability} = \frac{\text{Weight loss}}{\text{Weight of tablets before operation}} \text{x}100$$

d) In- vitro Dissolution Studies by U.V Spectrophotometer :

In-vitro drug release studies of Lurasidone was studied using dissolution apparatus USP XXI Rotating basket method pH 1.2(0.1N HCl) buffer 900 ml was used at the dissolution medium. Tablet was placed in a basket and rotated at a speed of 50 rpm maintained at a temperature of 37 ± 0.5^{o}C. One of the sample was withdrawn at periodic time interval of 5, 10, 15, 20, 25, 30mins and was made upto 10 ml with 0.1N HCl buffer solution. One ml of fresh dissolution medium was replaced after each time of withdrawn of sample. Followed by study in pH 7.4 phosphate buffer used in dissolution medium. the dissolution medium 1 ml were taken at an interval of 1, 2, 3, upto 12 hrs with replacement of equal volume of fresh dissolution medium. The sample was made upto 10 ml with buffer solution and its absorbance was measured at 230 nm. The amount of drug was calculated using standard graph.

f) Content Uniformity Test:

Standard preparation:

Prepare a solution of USP Lurasidone in water having a known concentration of about 10 mcg per ml.

Sample preparation of Lurasidone:

One tablet was finely powdered and dissolved in 70 ml water shake by mechanical means for 15 mts, dilute with water to volume, filter and discarding the first 20 ml of filtrate. Dilute 10ml of filtrate with water to 100ml and 10 ml of the resulting solution with water to 100 ml and measured the absorbance at 230 nm.

5.5 STABILITY STUDIES:

As per *in-vitro* release formulation F8 was found to be desirable than other formulations. Hence it was chosen for stability studies. The tablets were chamber (Ostwald Mumbai), 60^{o}C in incubator. At the interval of 1 month tablets were withdrawn and evaluated for physical properties like thickness, hardness, diameter, friability, weight variation and content uniformity. *In- vitro* drug release is also carried out.

5.6 DATA ANALYSIS:

To analyse the mechanism of release, the best formulation was subjected to some statistical tests.

Results of the data were fitted into the following equation.

- Zero order equation
- First order equation
- Higuchi plot
- Peppas plot

6. RESULTS AND DISCUSSION

The present study was undertaken to formulate Lurasidone bilayer tablets. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time. The short biological half-life and dosing frequency lesmore than one per day make the drug an ideal candidate for sustained release.

The tablets prepared in the present study by direct compression method have advantages over those prepared by wet granulation in terms of time and energy consumption , thus making it possible to formulate tablets at a lower cost. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery.

The study involved pre-formulation of drugs and granules, formulation and processing development along with evaluation of the tablets.

6.1 PRE-FORMULATION STUDY OF DRUG:

- The Lurasidone was subjected to drug-excipients compatibility study with excipients like hydroxyl propyl methyl cellulose, microcrystalline cellulose, croscarmellose, crospovidone, sodium lauryl sulphate, magnesium stearate, starch and talc. The mixtures shown to have no color change.
- The angle of repose for pure drug was very less and hence the poor flow of the pure drug was exhibited. Also the carr's index of the pure drug was found to be high, confirming that the drug has poor flow properties and compressibility.
- Good flow of powders / granules was improved by adding Excipients and is essential in tableting because the compressibility and flow properties of the drugs likely to influence the compression process in the preparation of tablets. In view of this the formulation were prepared by direct compression technique to improve the flow as well as compressibility.

Table: 7 Pre-formulation study data of the pure drug

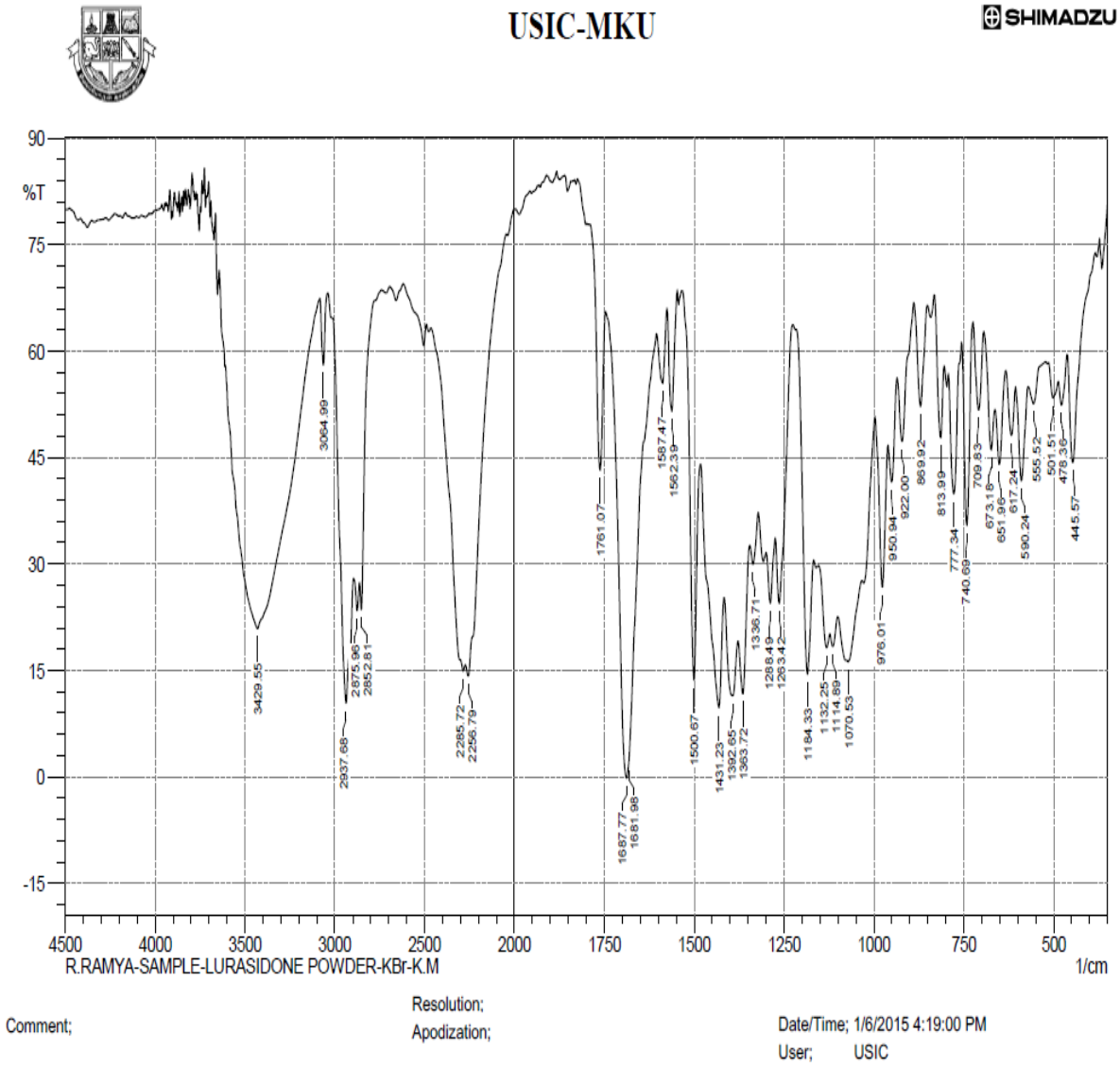
S.N	Parameters	Values obtained
1.	Angle of repose	10.28 ± 0.002
2.	Loss on drying	0.408 ± 0.005
3.	Bulk density (gm/ml)	0.3175 ± 0.006
4.	Tap density (gm/ml)	0.4286 ± 0.003
5.	Hausner ratio	1.3 ± 0.002
6.	Carr's index	26.18 ± 0.561

***Values mentioned are average of 3 determinations**

6.2 INFRA RED SPECTROSCOPIC STUDIES:

By using FTIR technique, Lurasidone and polymers like croscarmellose, crospovidone, hydroxyl propyl methyl cellulose, microcrystalline cellulose, sodium lauryl sulphate, starch, magnesium stearate, talc were identified by the frequency of obtained peaks.

The interpretation of the infra red spectrum of the drug and polymers are as follows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1250
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500
1/cm
3429.55
3064.99
2937.68
2875.96
2852.81
2285.72
2256.79
1761.07
1687.77
1681.98
1587.47
1562.39
1500.67
1431.23
1392.65
1363.72
1336.71
1288.49
1263.42
1184.33
1132.25
1114.89
1070.53
976.01
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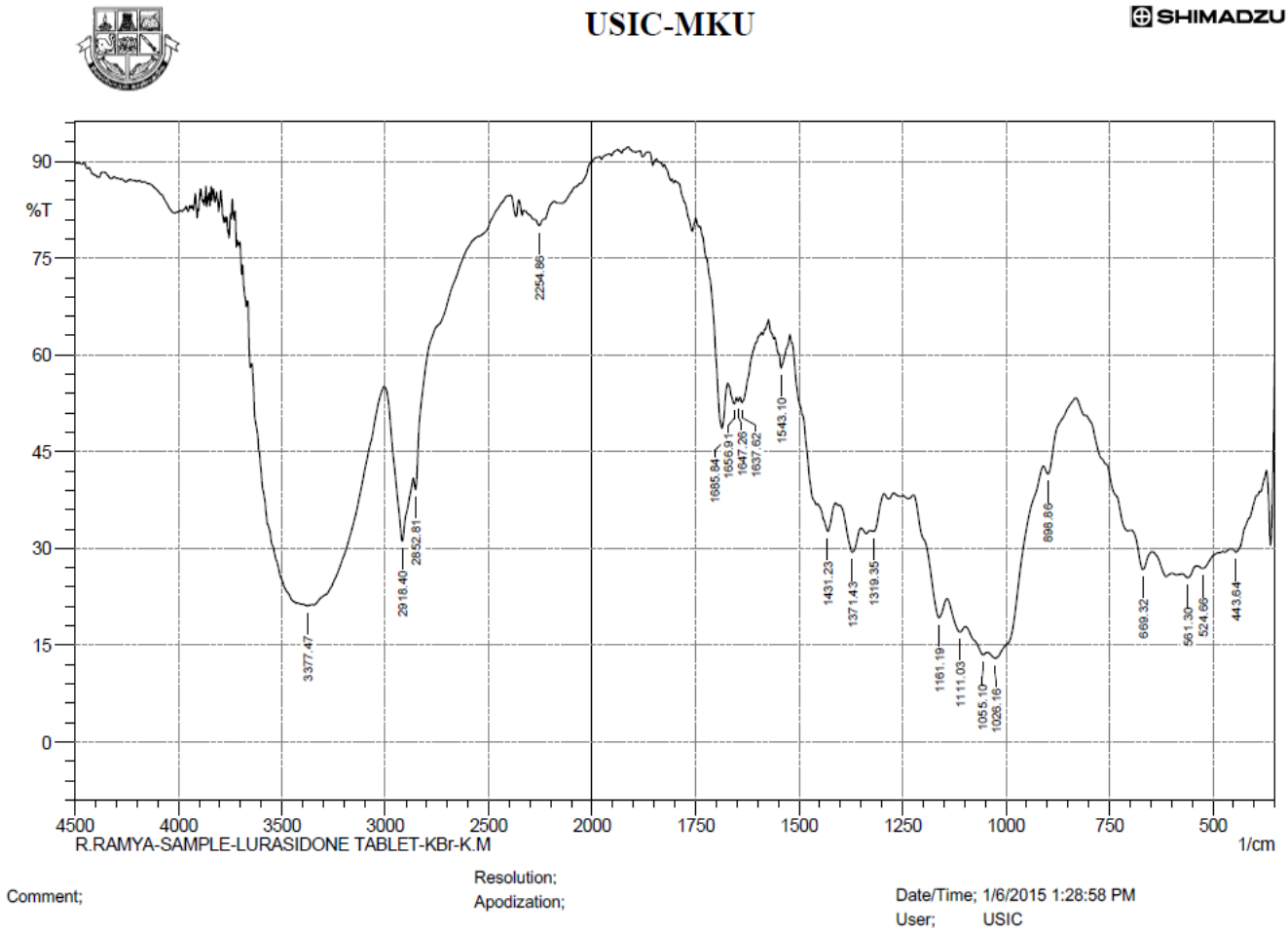
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750
500
1/cm
3377.47
2918.40
2852.81
2254.86
1685.84
1656.91
1647.26
1637.62
1543.10
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1026.16
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User; USIC

Table:8 IR spectra of pure Lurasidone:

Frequency (cm^{-1})	Groups Assigned
1263.42	N-H stretching
1681.96	C=C stretching
2256.79	S-H stretching
1761.07	C=O stretching
3429.55	C-H stretching

Table:9 IR spectra of optimized formulation:

Frequency (cm^{-1})	Groups Assigned
1026.16	N-H stretching
1685.84	C=C stretching
2254.86	S-H stretching
1760.08	C=O stretching
3377.47	C-H stretching

IR Report:

When FT IR Spectrum of Lurasidone (pure drug), excipients and optimized formulation of Lurasidone bilayer tablet (F8) were compared, there were no major changes in the position of the spectrum. It indicates absence of physical and chemical interaction among active component Lurasidone and excipients. So the bilayer tablet of Lurasidone has no interaction with added excipients.

6.3 EVALUATION OF POWER BLEND:

The prepared granules of the formulations were evaluated for the parameters like bulk density, tap density, compressibility index, hausner ratio, angle of repose and loss on drying.

- After granulation, angle of repose was improved.
- Hausner ratio was found to be 1.2 (or) less than 1.2
- Carr's index was found to be in the range of 12-16
- All these values indicated that the granules have good flow property and hence the granulation process has improved the flow property.

Table:10 Physical Characteristics of immediate release powder blend

Formulation Code	Angle of repose(Θ)	Loss on drying(%)	Bulk density(g/ml)	Tapped density(g/ml)	Hausner ratio	Carr's index
F_1	22.14±0.005	1.70±0.846	0.5562±0.011	0.6896±0.002	1.168±0.003	11.62±0.531
F_2	23.11±0.002	1.82±0.921	0.5742±0.012	0.6431±0.004	1.142±0.001	10.86±0.468
F_3	22.62±0.004	1.97±0.682	0.5842±0.011	0.6426±0.005	1.153±0.004	12.44±0.379

***Values mentioned are average of 3 determinations**

Table:11 Physical Characteristics of sustained release powder blend

Formulation Code	Angle of repose(Θ)	Loss on drying(%)	Bulk density(g/ml)	Tapped density(g/ml)	Hausner ratio	Carr's index
F_1	25.56±0.54	1.18±0.987	0.358±0.010	0.412±0.002	1.19±0.005	15.42±0.213
F_2	26.21±0.68	1.12±0.865	0.381±0.012	0.423±0.001	1.18±0.008	14.68±0.143
F_3	25.42±0.42	1.15±0.963	0.390±0.014	0.415±0.004	1.12±0.009	16.21±0.572
F_4	26.54±0.62	1.10±0.886	0.363±0.020	0.442±0.003	1.14±0.006	14.98±0.312
F_5	25.89±0.31	1.17±0.928	0.371±0.015	0.428±0.001	1.13±0.005	15.56±0.124
F_6	25.65±0.73	1.21±0.913	0.384±0.018	0.414±0.003	1.15±0.003	14.89±0.172
F_7	25.32±0.81	1.13±0.829	0.375±0.019	0.426±0.005	1.2±0.002	16.12±0.711
F_8	26.76±0.92	1.20±0.911	0.364±0.013	0.422±0.002	1.19±0.004	15.43±0.109
F_9	26.22±0.55	1.16±0.846	0.382±0.011	0.445±0.004	1.17±0.001	16.14±0.121

***Values mentioned are average of 3 determinations**

6.4 *IN-VITRO* RELEASE STUDIES:

6.4.1 *IN-VITRO* RELEASE OF IMMEDIATE RELEASE LAYER:

In formulation F_1 formulation only croscarmellose sodium 10mg was used and release was found to be 14.58%. Hence, to get more release it was decided to alter the formulation further.

In formulation F_2 crospovidone 10mg was used and release was found to be 18.09%. In F_3 formulation , combination of croscarmellose 10mg and crospovidone 10mg was used and release was found to be 29.66% at 30 minutes. The percentage of drug release increased with combination of super disintegrants like croscarmellose sodium and crospovidone which may be due to its strong swelling property and highly porous structure of crospovidone.

Table:12Dissolution data of F1 Formulation:

S.No	Time (mins)	Amount of drug release (mg)	Cummulative % drug release
1	5	1.8	4.5
2	10	3.6	9.03
3	15	4.8	12.05
4	20	5.4	13.57
5	25	5.6	14.08
6	30	5.8	14.58

Fig:3 Dissolution profile of F_1 Formulation:

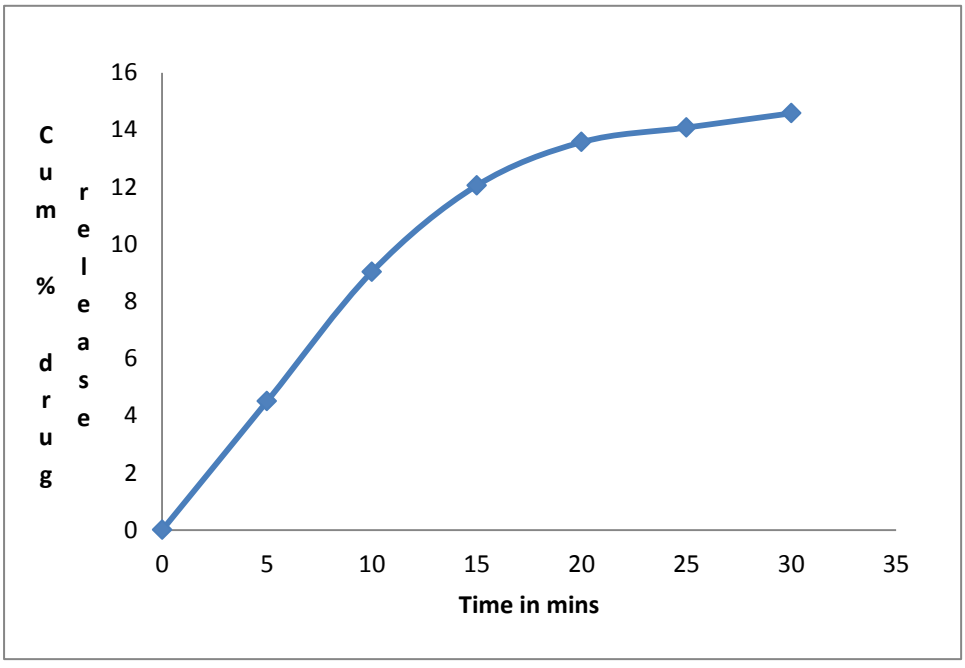


Table:13 Dissolution data of F_2 Formulation:

S.No	Time (mins)	Amount of drug release (mg)	Cummulative % drug release
1	5	2.3	5.75
2	10	4.7	11.78
3	15	5.8	14.57
4	20	6.1	15.33
5	25	6.8	17.08
6	30	7.2	18.09

Fig:4 Dissolution profile of F_2 Formulation

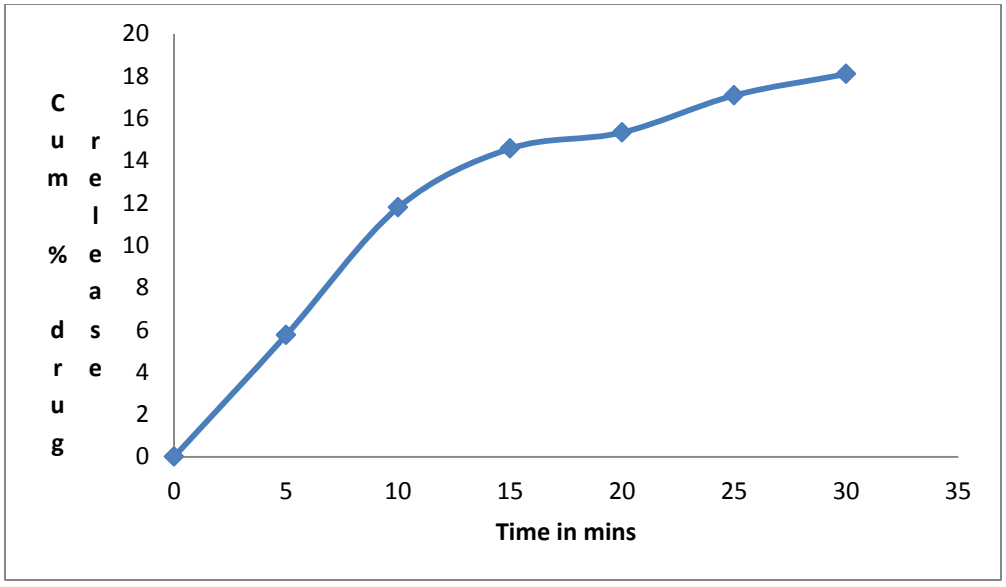
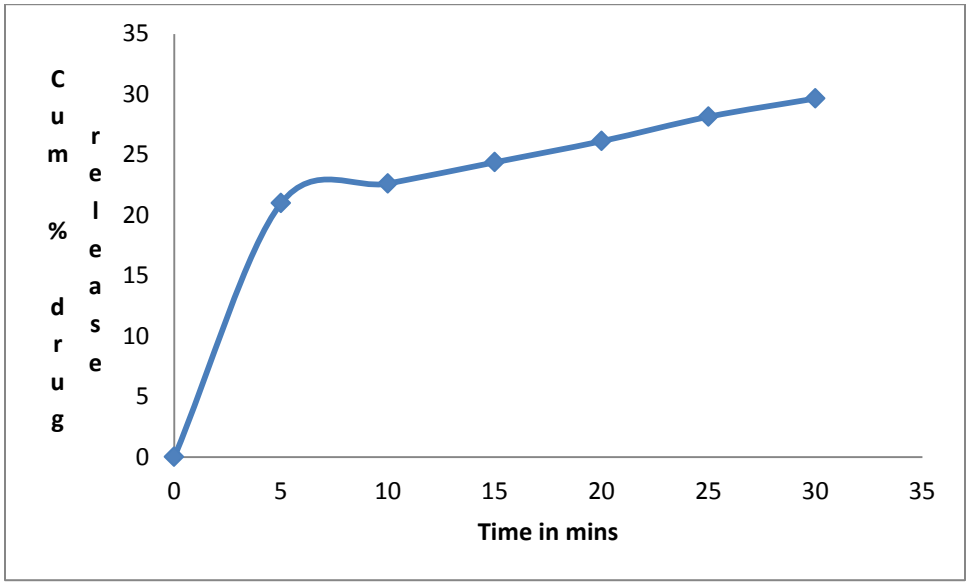


Table:14 Dissolution data of F_3 Formulation:

S.No	Time (mins)	Amount of drug release (mg)	Cummulative % drug release
1	5	8.4	21.0
2	10	9.0	22.62
3	15	9.7	24.38
4	20	10.4	26.13
5	25	11.2	28.15
6	30	11.8	29.66

Fig:5 Dissolution profile of F_3 Formulation



6.4.2 *IN-VITRO* RELEASE OF SUSTAINED RELEASE LAYER:

In F_1, F_2 formulations HPC in various concentration 14, 28 mg was used and release was found to be at the end of 24^{th} hrs 85.05%, 86.85% respectively. In F_3, F_4, F_5 formulations HPMC (K4) in various concentration 14,28, 42 mg was used and release was found to be at the end of 24^{th} hrs 87.78%, 90.48% , 92.3% respectively.

HPMC (K4M) and HPMC (K100) was selected for further formulation to increase the release of drug.

In F_6, F_7, F_8 formulations HPMC (K4M) and HPMC (K100) in various concentration 14,28, 42 mg was used and release was found to be at the end of 24^{th} hrs 94.1% , 96.825%, 99.53% respectively.

In F_9 formulation HPMC (K4M) and HPMC (K100) in concentration 56 mg was used and release was found to be at the end of 24^{th} hrs 99.53%. F_8 formulation and F_9 formulation *in-vitro* release profile have shown the same release at 24 hours. But F_8 formulation shows the(99.53%) good release at minimum concentration of HPMC(84mg). So the formulation F_8 was the optimized one.

Table:15 Dissolution data of F_1 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	12.24	30.8
2	2	13.24	33.27
3	3	14.04	35.28
4	4	14.99	37.67
5	5	15.84	39.8
6	6	17.34	43.57
7	7	18.0	45.23
8	8	19.4	48.75
9	9	20.16	50.65
10	10	21.01	52.80
11	11	21.96	55.18
12	12	23.44	58.91
13	13	25.92	65.1
14	14	27.11	68.13
15	15	28.08	70.55
16	16	28.80	72.39
17	17	29.16	73.3
18	18	29.98	75.35
19	19	30.24	76.01
20	20	30.89	77.64
21	21	31.64	79.52
22	22	32.76	82.33
23	23	33.11	83.23
24	24	33.84	85.05

Fig:6 Dissolution profile of F_1 Formulation:

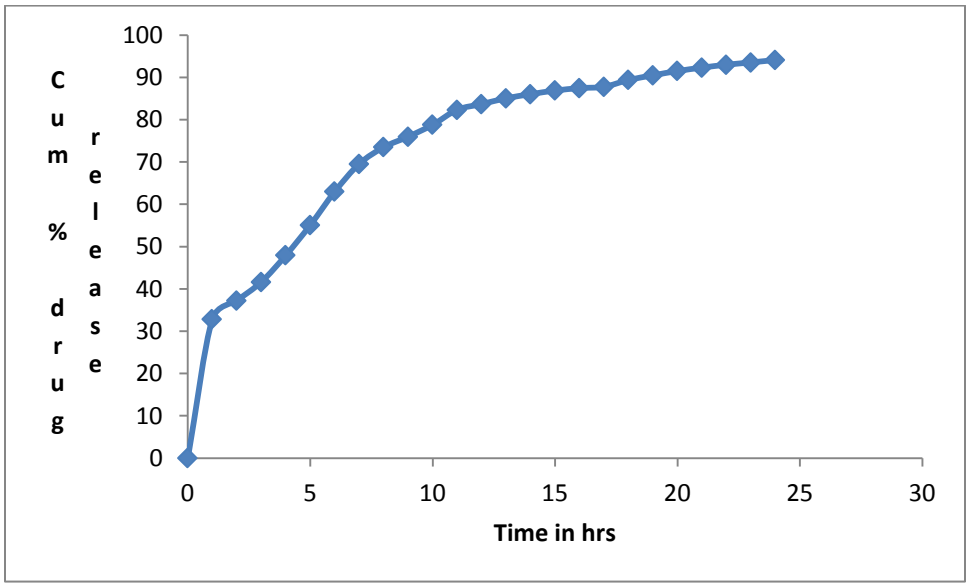


Table:16 Dissolution data of F_2 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	12.24	30.80
2	2	12.45	31.29
3	3	12.96	32.58
4	4	13.44	33.78
5	5	14.04	35.28
6	6	14.98	37.14
7	7	15.84	39.80
8	8	17.10	42.97
9	9	18.01	45.23
10	10	19.64	49.35
11	11	20.16	50.65
12	12	20.94	52.63
13	13	21.96	55.18
14	14	23.84	59.90
15	15	25.92	65.10
16	16	27.22	68.41
17	17	28.08	70.55
18	18	28.88	72.59
19	19	29.16	73.30
20	20	30.55	76.78
21	21	31.76	79.82
22	22	32.44	81.54
23	23	33.24	83.55
24	24	34.56	86.85

Fig:7 Dissolution profile of F_2 Formulation:

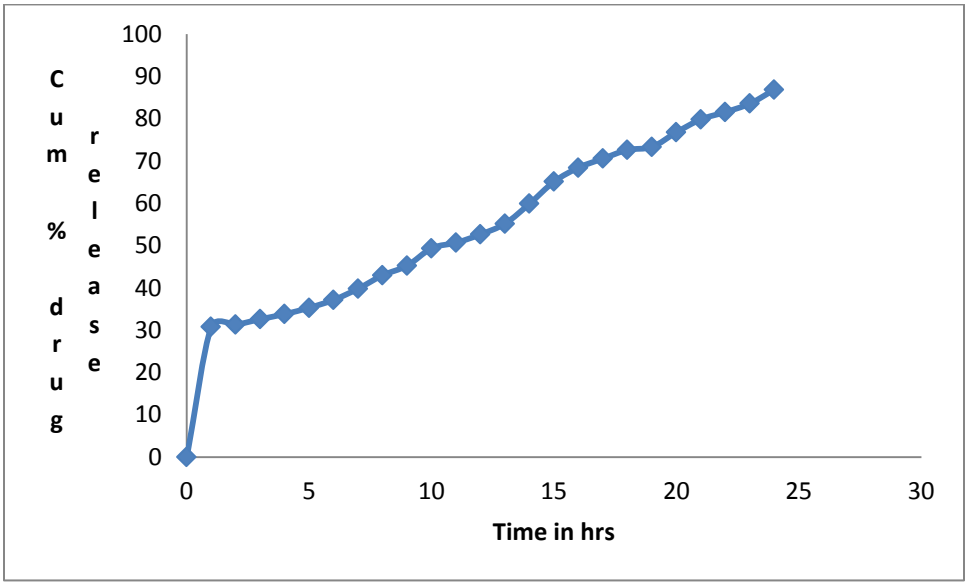


Table:17 Dissolution data of F_3 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	14.04	35.28
2	2	15.02	37.74
3	3	15.84	39.8
4	4	17.83	44.79
5	5	18.0	45.23
6	6	19.68	49.45
7	7	20.16	50.65
8	8	21.01	52.80
9	9	21.96	55.18
10	10	23.88	60.01
11	11	25.92	65.1
12	12	27.44	68.96
13	13	28.08	70.55
14	14	29.45	74.01
15	15	30.24	75.98
16	16	31.46	79.07
17	17	32.76	82.33
18	18	33.10	83.20
19	19	33.84	85.05
20	20	34.04	85.57
21	21	34.56	86.88
22	22	34.64	87.08
23	23	34.78	87.43
24	24	34.92	87.78

Fig:8 Dissolution profile of F_3 Formulation:

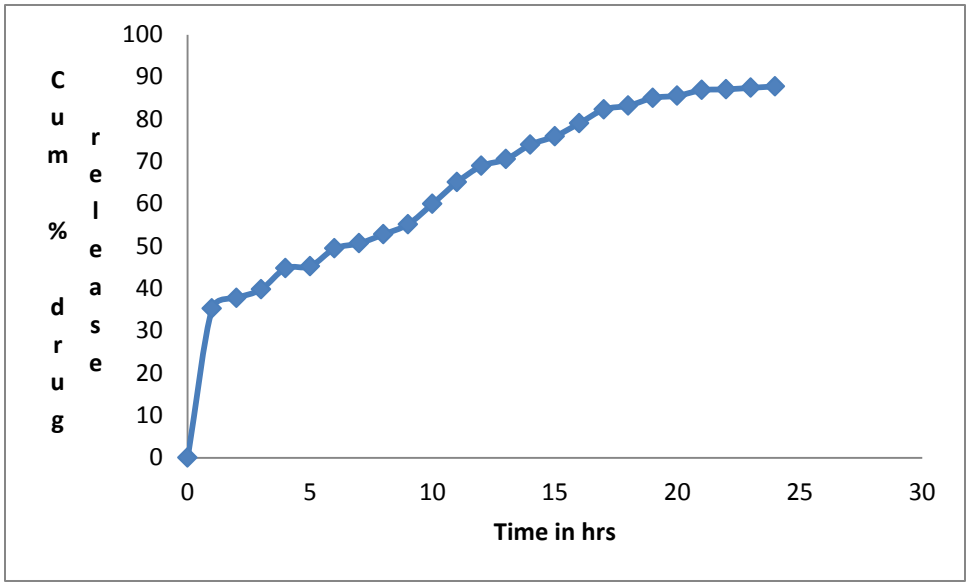


Table:18 Dissolution data of F_4 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	15.84	39.60
2	2	17.24	43.32
3	3	18.01	45.23
4	4	19.22	48.30
5	5	20.16	50.65
6	6	21.12	53.08
7	7	21.96	55.18
8	8	23.84	59.91
9	9	25.92	65.10
10	10	27.66	69.51
11	11	28.08	70.55
12	12	29.78	74.84
13	13	30.24	75.98
14	14	31.84	80.02
15	15	32.76	82.33
16	16	33.01	82.98
17	17	33.84	85.05
18	18	34.09	85.69
19	19	34.56	86.88
20	20	34.92	87.78
21	21	35.12	88.28
22	22	35.98	90.43
23	23	36.0	90.49
24	24	36.1	90.75

Fig:9 Dissolution profile of F_4 Formulation:

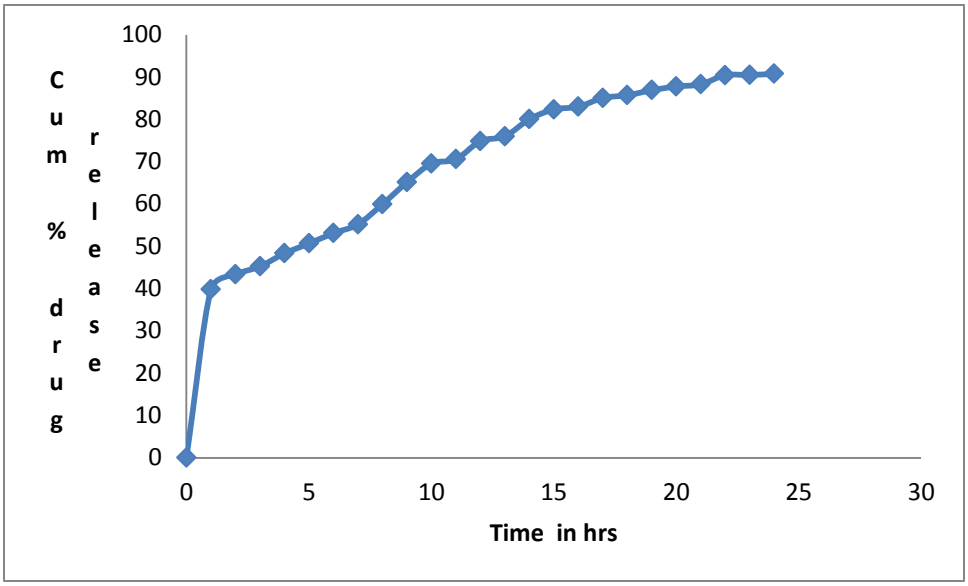


Table: 19 Dissolution data of F_5 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	15.94	39.85
2	2	18.64	46.82
3	3	20.16	50.63
4	4	21.10	53.03
5	5	21.96	55.18
6	6	23.75	59.68
7	7	25.92	65.10
8	8	27.44	68.96
9	9	28.08	70.55
10	10	29.21	73.41
11	11	30.24	75.98
12	12	31.55	79.29
13	13	32.76	82.33
14	14	33.14	83.31
15	15	33.84	85.05
16	16	34.09	85.69
17	17	34.56	86.88
18	18	34.71	87.25
19	19	34.92	87.78
20	20	35.24	88.58
21	21	35.86	90.13
22	22	36.01	90.48
23	23	36.46	91.65
24	24	36.72	92.30

Fig:10 Dissolution profile of F_5 Formulation:

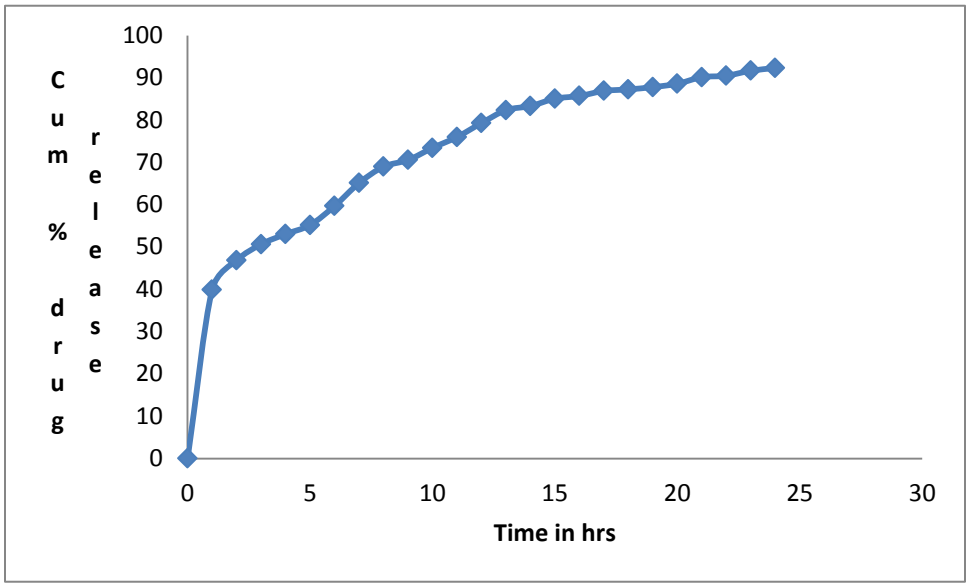


Table: 20 Dissolution data of F_6 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	13.14	32.85
2	2	14.81	37.22
3	3	16.56	41.63
4	4	19.08	47.93
5	5	21.92	55.08
6	6	25.07	62.98
7	7	27.68	69.55
8	8	29.24	73.49
9	9	30.22	75.98
10	10	31.35	78.79
11	11	32.76	82.33
12	12	33.29	83.68
13	13	33.84	85.05
14	14	34.22	86.02
15	15	34.56	86.88
16	16	34.79	87.45
17	17	34.92	87.78
18	18	35.56	89.38
19	19	36.0	90.48
20	20	36.4	91.5
21	21	36.72	92.3
22	22	36.99	92.99
23	23	37.21	93.53
24	24	37.44	94.1

Fig:11 Dissolution profile of F_6 Formulation:

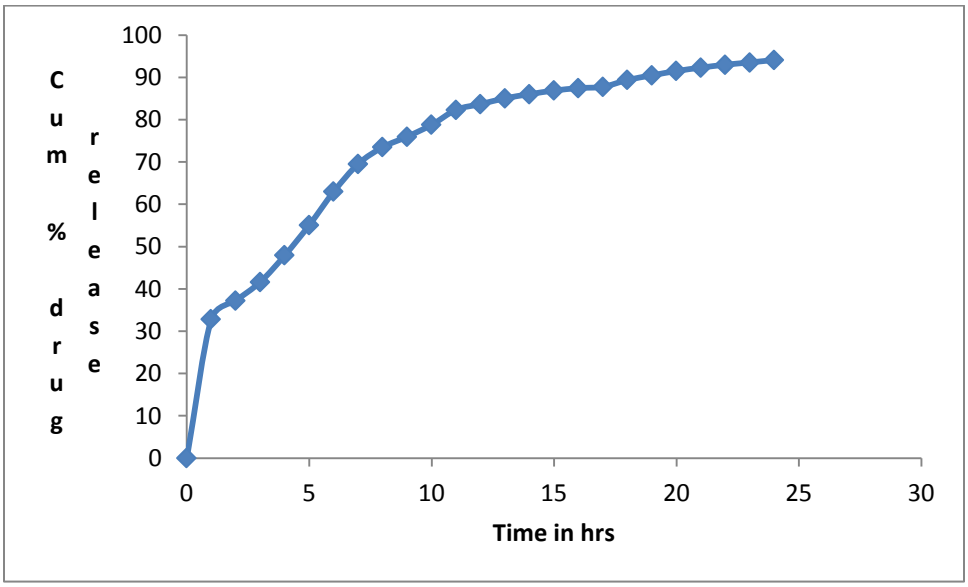


Table: 21 Dissolution data of F_7 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	13.51	33.78
2	2	15.29	38.42
3	3	17.35	43.56
4	4	19.27	48.44
5	5	21.13	53.11
6	6	23.43	58.88
7	7	25.30	63.58
8	8	26.87	67.54
9	9	28.57	71.82
10	10	31.24	78.51
11	11	32.44	81.54
12	12	33.28	83.65
13	13	33.79	84.93
14	14	34.15	85.84
15	15	34.92	87.77
16	16	35.58	89.43
17	17	36.0	90.49
18	18	36.41	91.52
19	19	36.72	92.3
20	20	37.02	93.06
21	21	37.80	95.0
22	22	38.13	95.85
23	23	38.32	96.32
24	24	38.52	96.83

Fig:12 Dissolution profile of F_7 Formulation:

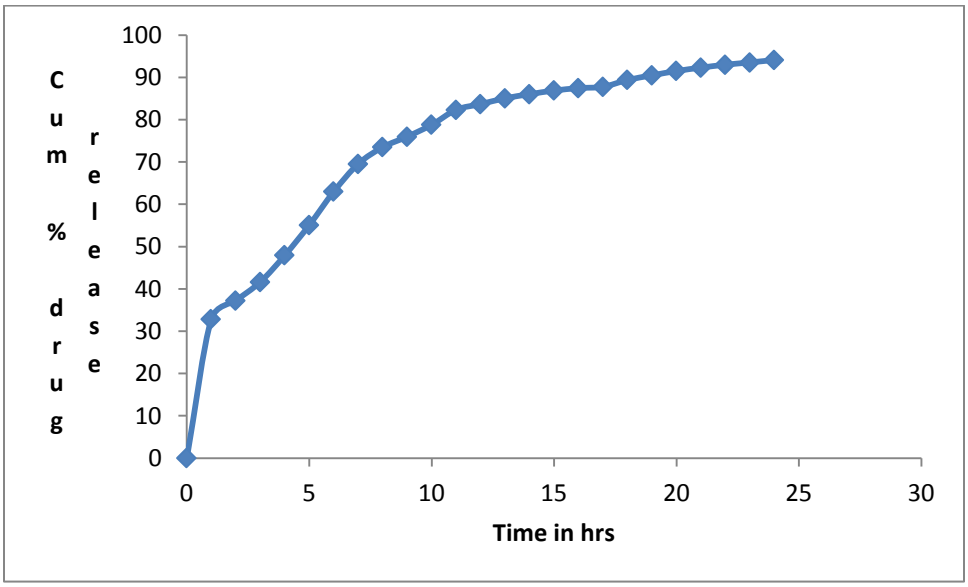


Table: 22 Dissolution data of F_8 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	14.28	34.70
2	2	14.81	37.21
3	3	16.03	40.28
4	4	17.25	43.34
5	5	18.34	46.10
6	6	19.41	48.76
7	7	20.43	51.35
8	8	21.44	53.88
9	9	21.96	55.20
10	10	22.85	57.42
11	11	23.95	60.20
12	12	25.36	63.74
13	13	26.88	67.54
14	14	28.64	71.98
15	15	29.79	74.86
16	16	31.25	78.53
17	17	32.49	81.65
18	18	33.77	84.87
19	19	34.87	87.64
20	20	36.02	90.54
21	21	37.27	93.67
22	22	37.96	95.42
23	23	38.93	97.86
24	24	39.77	99.97

Fig:13 Dissolution profile of F_8 Formulation:

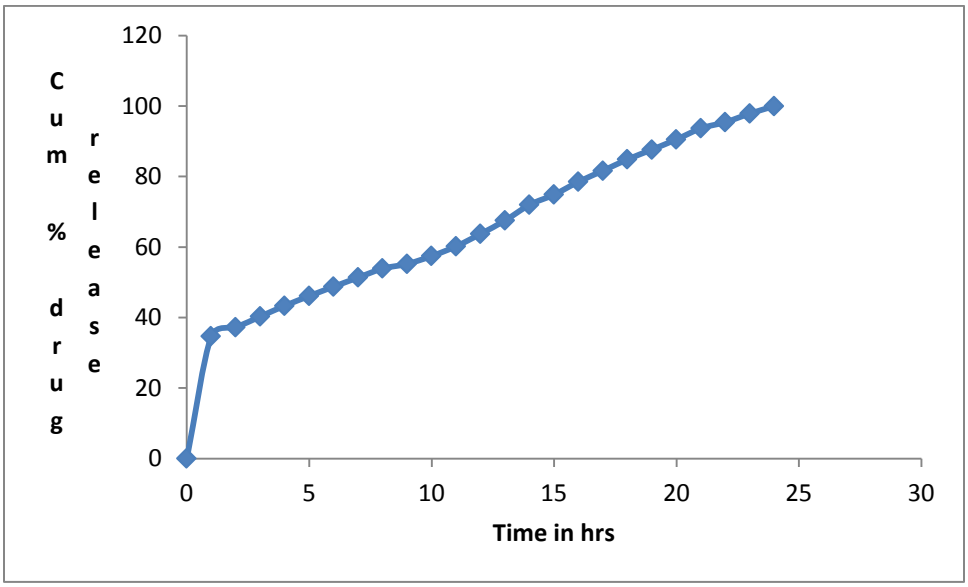
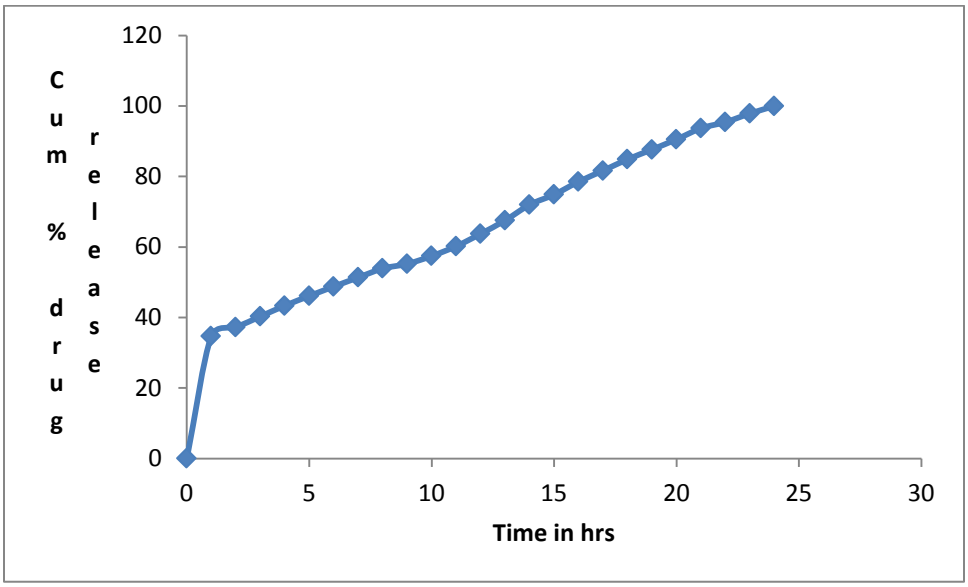


Table:23 Dissolution data of F_9 Formulation:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	14.28	34.70
2	2	14.81	37.21
3	3	16.03	40.28
4	4	17.25	43.34
5	5	18.34	46.10
6	6	19.41	48.76
7	7	20.43	51.35
8	8	21.44	53.88
9	9	21.96	55.20
10	10	22.85	57.42
11	11	23.95	60.20
12	12	25.36	63.74
13	13	26.88	67.54
14	14	28.64	71.98
15	15	29.79	74.86
16	16	31.25	78.53
17	17	32.49	81.65
18	18	33.77	84.87
19	19	34.87	87.64
20	20	36.02	90.54
21	21	37.27	93.67
22	22	37.96	95.42
23	23	38.93	97.86
24	24	39.77	99.97

Fig:14 Dissolution profile of F_9 Formulation



6.5 EVALUATION OF TABLETS:

a)Thickness and Diameter:

The thickness and diameter were found in the range of 6.0 ± 0.024 to 6.5 ± 0.048 and 12.2 ± 0.047 to 12.9 ± 0.048 respectively.

Table:24 Thickness and Diameter data of the Tablets:

Formulation Code	Thickness (mm) ± S.D	Diameter (mm) ± S.D
F_1	6.3 ±0.024	12.5 ±0.048
F_2	6.1 ±0.04	12.2 ±0.049
F_3	6.0 ±0.048	12.3 ±0.04
F_4	6.3 ±0.024	12.1 ±0.06
F_5	6.5 ±0.048	12.2 ±0.024
F_6	6.1 ±0.09	12.1 ±0.048
F_7	6.0 ±0.024	12.93±0.047
F_8	6.1 ±0.004	12.2 ±0.076
F_9	6.1 ±0.048	12.2 ±0.042

b)Weight Variation, Hardness and Friability:

Depending upon the ingredients of different formulations, the weight of the tablet was fixed. In each formulation, weight variation was within the I.P limit. Mostly, the variation was within ± 5%. The hardness of the different formulations ranged from 4-7 kg / cm^2. All the formulations exhibited less than 1% friability.

Table:25 Hardness, weight variation and Friability data of the Tablets:

Formulation Code	Weight variation (mg)± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D
F_1	585±2.710	6.8±0.244	0.31±0.02
F_2	600±1.962	6.4±0.251	0.26±0.04
F_3	615±2.6	6.3±0.244	0.36±0.03
F_4	595±3.71	6.7±0.244	0.36±0.037
F_5	600±4.5	6.5±0.048	0.33±0.014
F_6	610±3.92	6.3±0.447	0.30±0.009
F_7	615±4.87	6.2±0.244	0.33±0.014
F_8	625±4.62	6.1±0.316	0.33±0.009
F_9	610±3.81	6.2±0.244	0.40±0.04

c) Content Uniformity:

The results for content uniformity are presented in following table. The results were found to be within the limits (98 to 99.78%). It shows that the drug was uniformly distributed throughout the tablets.

Table:26 Content Uniformity data of the Tablets:

Formulation Code	Content Uniformity in Percentage ± S.D
F_1	99.18±0.24
F_2	99.13±0.115
F_3	98.67±0.08
F_4	99.22±0.37
F_5	98.56±0.43
F_6	98.42±0.10
F_7	99.15±0.22
F_8	99.20±0.20
F_9	98.89±0.115

6.6 STABILITY STUDIES:

The optimized F_8 formulation was subjected to accelerated stability conditions for 3 months at 25°C /60% RH, 30°C/75%RH, 40°C/75% RH in a stability chamber (Osworld, Mumbai). At the interval of 1 month tablets were withdrawn and evaluated for various parameters like thickness, diameter, weight variation, hardness and content uniformity. The tablets did not show any variation in the tested parameters and the results are within the limits.

Table:27 Comparison of physical parameters for optimized formulation F_8 and stability study data S_1 batch:

S.No	Parameters	F_8	25°C / 60% RH		
			At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1	Thickness(mm)	6.1±0.048	6.1±0.047	6.2±0.038	6.3±0.038
2	Diameter(mm)	12.2±0.048	12.1±0.042	12.1±0.045	12.1±0.047
3	Hardness(kg/cm^2)	6.2±0.244	6.2±0.045	6.2±0.221	6.2±0.115
4	Friability(%)	0.40±0.009	0.4±0.009	0.4±0.009	0.41±0.008
5	Weight Variation(mg)	615±3.185	617±3.115	618±3.525	617±3.251
6	Content Uniformity	99.20±0.115	99.10±0.11	99.72±0.112	99.7±0.11

***** $F_{8:}$ Optimized formulation

*S_1: Formulation F_8 kept for stability study at temperature 25°C / 60% RH

Table:28 Comparison of physical parameters for optimized formulation F_8 and stability study data S_1 batch:

S.No	Parameters	F_8	30°C / 75% RH		
			At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1	Thickness(mm)	6.1±0.048	6.1±0.047	6.1±0.048	6.1±0.038
2	Diameter(mm)	12.2±0.048	12.5±0.042	12.3±0.045	12.3±0.047
3	Hardness(kg/cm^2)	6.2±0.244	6.1±0.045	6.1±0.221	6.0±0.115
4	Friability(%)	0.40±0.009	0.43±0.007	0.43±0.009	0.42±0.008
5	Weight Variation(mg)	615±3.185	613±3.115	613±3.525	612±3.251
6	Content Uniformity	99.20±0.115	99.09±0.11	99.08±0.112	99.0±0.11

***** $F_{8:}$ Optimized formulation

*S_1: Formulation F_8 kept for stability study at temperature 30°C / 75% RH

Table:29 Comparison of physical parameters for optimized formulation F_8 and stability study data S_1 batch:

S.No	Parameters	F_8	40^oC / 75% RH		
			At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1	Thickness(mm)	6.1±0.048	6.1±0.047	6.1±0.048	6.1±0.038
2	Diameter(mm)	12.2±0.048	12.1±0.042	12.3±0.045	12.3±0.047
3	Hardness(kg/cm^2)	6.2±0.244	6.3±0.045	6.2±0.221	6.0±0.115
4	Friability(%)	0.40±0.009	0.45±0.007	0.44±0.009	0.42±0.008
5	Weight Variation(mg)	615±3.185	617±3.115	615±3.525	612±3.251
6	Content Uniformity	99.20±0.115	99.15±0.11	99.09±0.112	99.0±0.11

* F_8: Optimized formulation

*S_1: Formulation F_8 kept for stability study at temperature 40^oC/75% RH

Table:30 Dissolution data of F_8 Formulation at 25°C / 60% RH after 1st month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	14.28	34.70
2	2	14.81	37.21
3	3	16.03	40.28
4	4	17.25	43.34
5	5	18.34	46.10
6	6	19.41	48.76
7	7	20.43	51.35
8	8	21.44	53.88
9	9	21.96	55.20
10	10	22.85	57.42
11	11	23.95	60.20
12	12	25.36	63.74
13	13	26.88	67.54
14	14	28.64	71.98
15	15	29.79	74.86
16	16	31.25	78.53
17	17	32.49	81.65
18	18	33.77	84.87
19	19	34.87	87.64
20	20	36.02	90.54
21	21	37.27	93.67
22	22	37.96	95.42
23	23	38.93	97.86
24	24	39.77	99.97

Fig:15 Dissolution profile of F_8 Formulation at 25°C / 60% RH after 1st month::

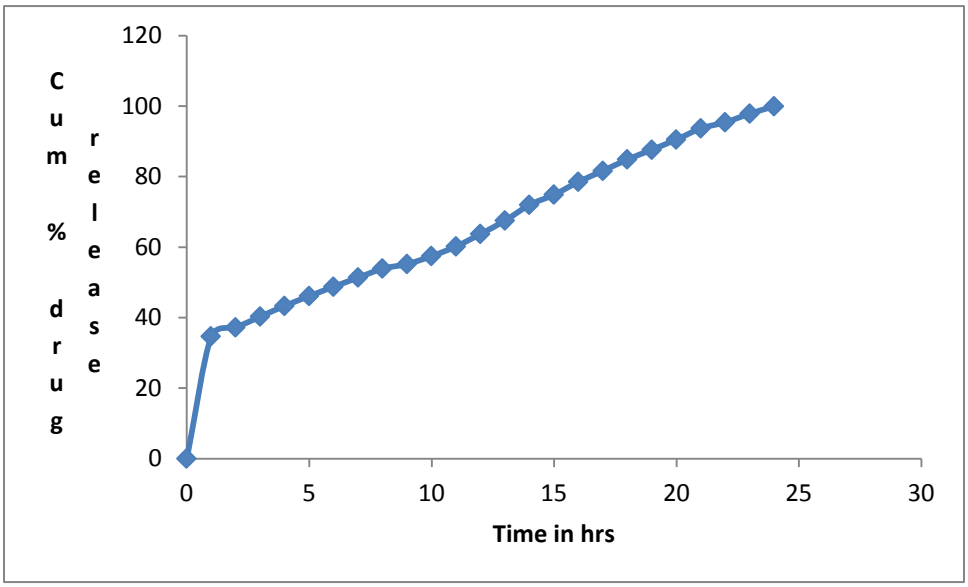


Table:31 Dissolution data of F_8 Formulation at 30°C / 75% RH after 1st month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	14.28	34.70
2	2	14.81	37.21
3	3	16.03	40.28
4	4	17.25	43.34
5	5	18.34	46.10
6	6	19.41	48.76
7	7	20.43	51.35
8	8	21.44	53.88
9	9	21.96	55.20
10	10	22.85	57.42
11	11	23.95	60.20
12	12	25.36	63.74
13	13	26.88	67.54
14	14	28.64	71.98
15	15	29.79	74.86
16	16	31.25	78.53
17	17	32.49	81.65
18	18	33.77	84.87
19	19	34.87	87.64
20	20	36.02	90.54
21	21	37.27	93.67
22	22	37.96	95.42
23	23	38.93	97.86
24	24	39.77	99.97

Fig:16 Dissolution profile of F_8 Formulation at 40^oC / 75% RH after 1^{st} month:

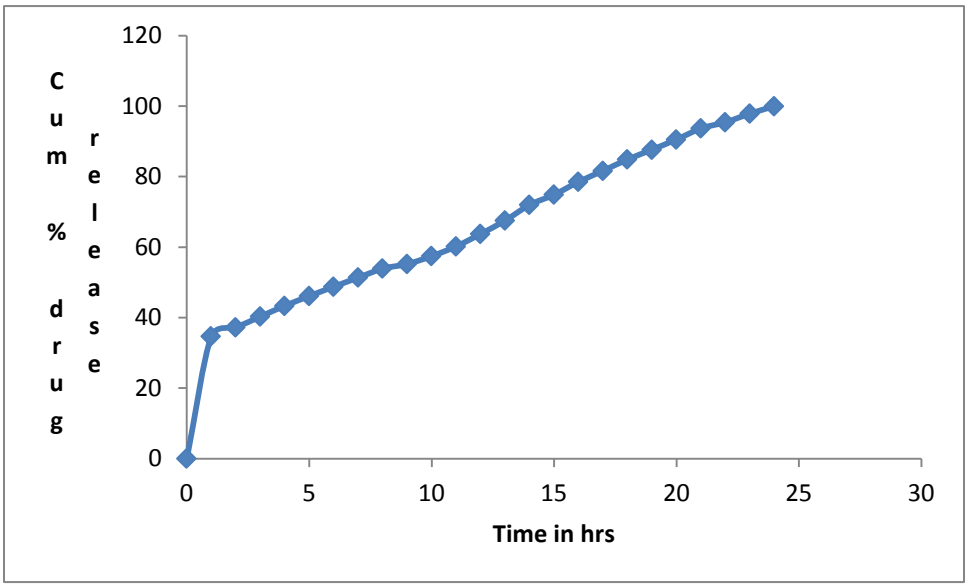


Table:32 Dissolution data of F_8 Formulation at 40°C / 75% RH after 1st month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	13.88	34.70
2	2	14.81	37.21
3	3	16.03	40.28
4	4	17.25	42.34
5	5	18.34	45.10
6	6	19.41	47.76
7	7	20.43	50.35
8	8	21.44	52.88
9	9	21.96	54.20
10	10	22.85	56.42
11	11	23.95	59.20
12	12	25.36	63.42
13	13	26.88	66.56
14	14	28.64	70.98
15	15	29.79	74.11
16	16	31.25	77.52
17	17	32.49	80.65
18	18	33.77	82.87
19	19	34.87	86.64
20	20	36.02	89.54
21	21	37.27	93.27
22	22	37.96	95.01
23	23	38.93	97.22
24	24	39.77	99.97

Fig:17 Dissolution profile of F_8 Formulation at 40^oC / 75% RH after 1^{st} month::

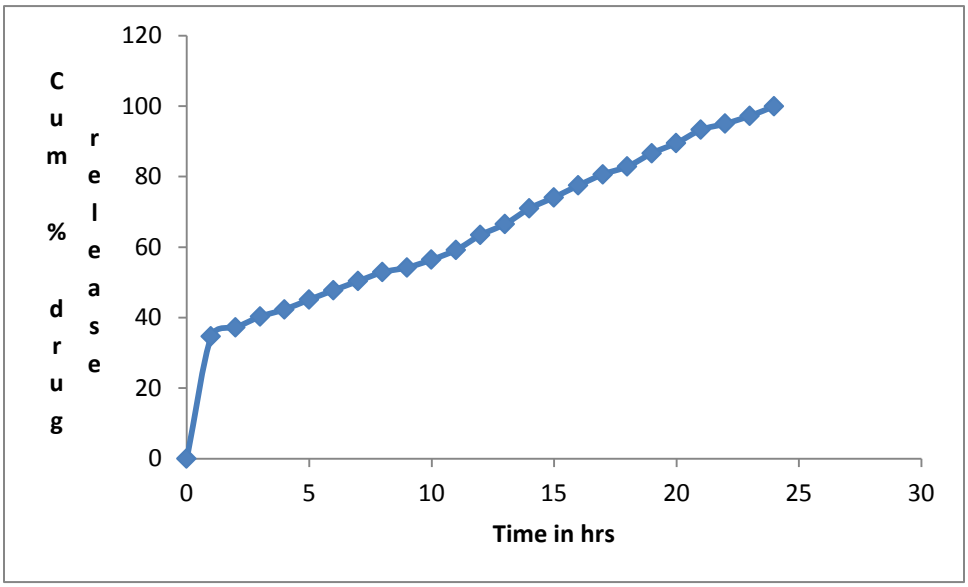


Table:33 Dissolution data of F_8 Formulation at 25°C / 60% RH after 2nd month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	14.28	34.70
2	2	14.81	37.21
3	3	16.03	40.28
4	4	17.25	43.34
5	5	18.34	46.10
6	6	19.41	48.76
7	7	20.43	51.35
8	8	21.44	53.88
9	9	21.96	55.20
10	10	22.85	57.42
11	11	23.95	60.20
12	12	25.36	63.74
13	13	26.88	67.54
14	14	28.64	71.98
15	15	29.79	74.86
16	16	31.25	78.53
17	17	32.49	81.65
18	18	33.77	84.87
19	19	34.87	87.64
20	20	36.02	90.54
21	21	37.27	93.67
22	22	37.96	95.42
23	23	38.93	97.86
24	24	39.77	99.97

Fig:18 Dissolution profile of F_8 Formulation at 25^oC / 60% RH after 2^{nd} month::

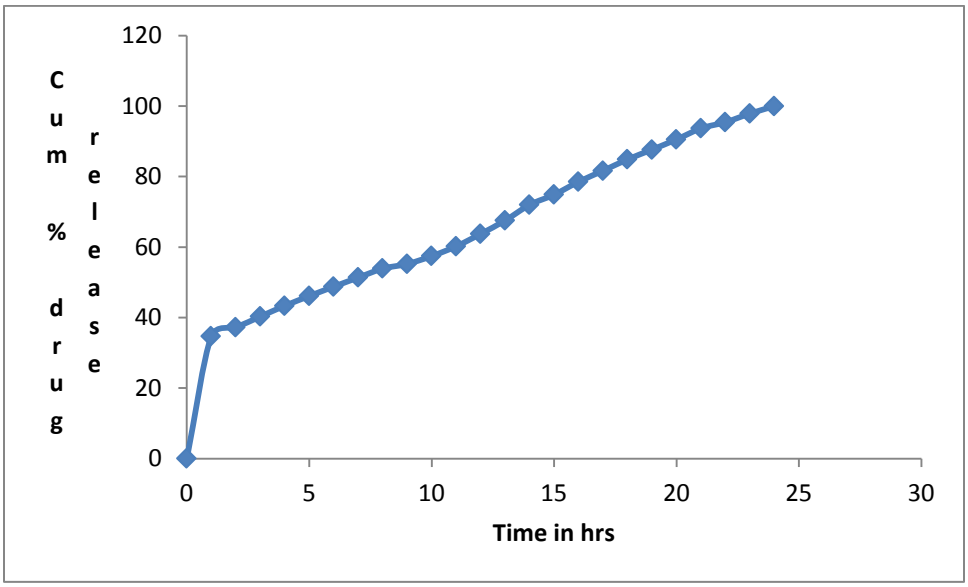


Table:34 Dissolution data of F_8 Formulation at 30°C / 75% RH after 2nd month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	13.51	33.78
2	2	15.29	38.42
3	3	17.35	43.56
4	4	19.27	48.44
5	5	21.13	53.11
6	6	23.43	58.88
7	7	25.30	63.58
8	8	26.87	67.54
9	9	28.57	71.82
10	10	31.24	78.51
11	11	32.44	81.54
12	12	33.28	83.65
13	13	33.79	84.93
14	14	34.15	85.84
15	15	34.92	87.77
16	16	35.58	89.43
17	17	36.0	90.49
18	18	36.41	91.52
19	19	36.72	92.3
20	20	37.02	93.06
21	21	37.80	95.0
22	22	38.13	95.85
23	23	38.32	96.32
24	24	38.52	96.83

Fig:19 Dissolution profile of F_8 Formulation at 30^oC / 75% RH after 2^{nd} month:

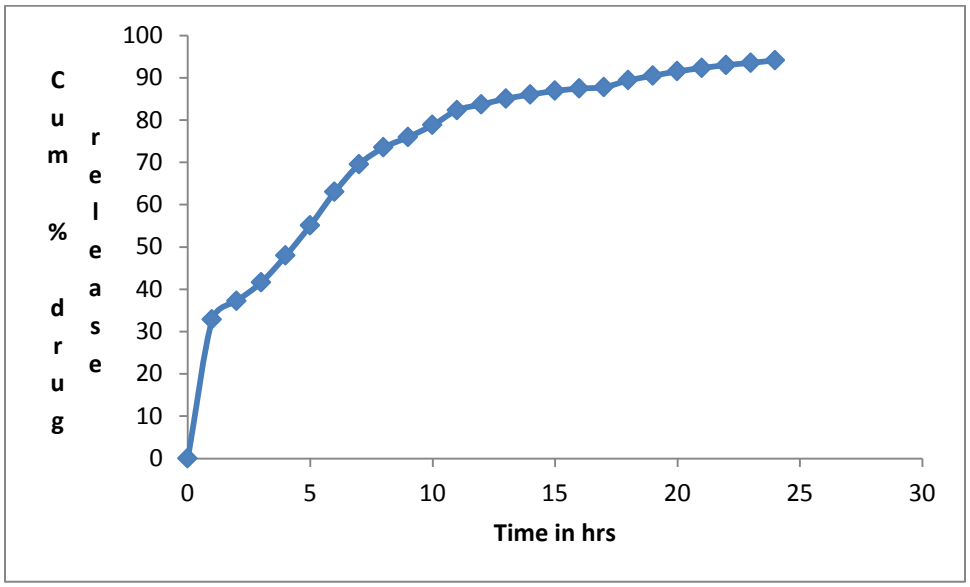


Table:35 Dissolution data of F_8 Formulation at 40^oC / 75% RH after 2^{nd} month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	13.51	33.78
2	2	15.29	38.42
3	3	17.35	43.56
4	4	19.27	48.44
5	5	21.13	53.11
6	6	23.43	58.88
7	7	25.30	63.58
8	8	26.87	67.54
9	9	28.57	71.82
10	10	31.24	78.51
11	11	32.44	81.54
12	12	33.28	83.65
13	13	33.79	84.93
14	14	34.15	85.84
15	15	34.92	87.77
16	16	35.58	89.43
17	17	36.0	90.49
18	18	36.41	91.52
19	19	36.72	92.3
20	20	37.02	93.06
21	21	37.80	95.0
22	22	38.13	95.85
23	23	38.32	96.32
24	24	38.52	96.83

Fig:20 Dissolution profile of F_8 Formulation at 40^oC / 75% RH after 2^{nd} month:

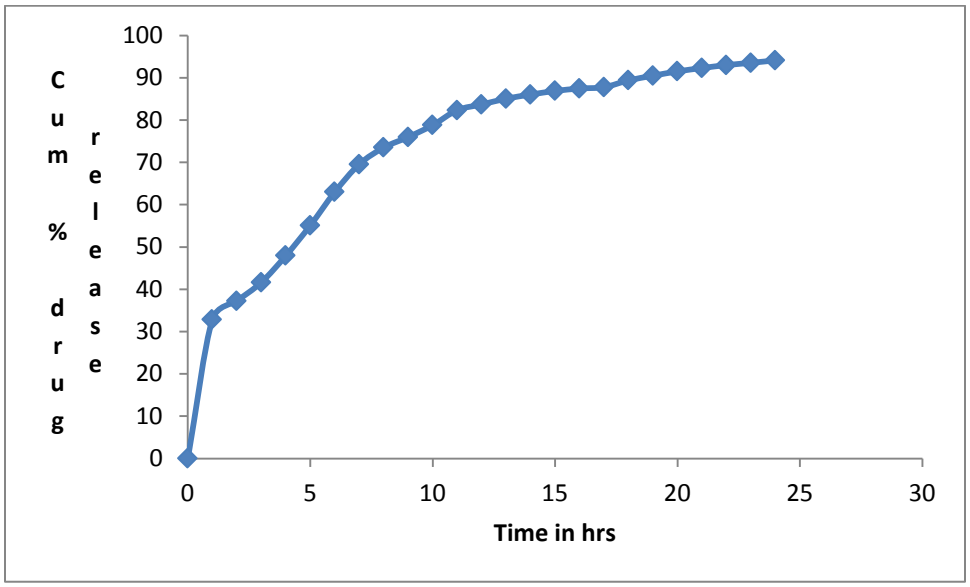


Table:36 Dissolution data of F_8 Formulation at 25°C / 60% RH after 3rd month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	14.28	34.70
2	2	14.81	37.21
3	3	16.03	40.28
4	4	17.25	43.34
5	5	18.34	46.10
6	6	19.41	48.76
7	7	20.43	51.35
8	8	21.44	53.88
9	9	21.96	55.20
10	10	22.85	57.42
11	11	23.95	60.20
12	12	25.36	63.74
13	13	26.88	67.54
14	14	28.64	71.98
15	15	29.79	74.86
16	16	31.25	78.53
17	17	32.49	81.65
18	18	33.77	84.87
19	19	34.87	87.64
20	20	36.02	90.54
21	21	37.27	93.67
22	22	37.96	95.42
23	23	38.93	97.86
24	24	39.77	99.97

Fig:21 Dissolution profile of F_8 Formulation at 25°C / 60% RH after 3rd month::

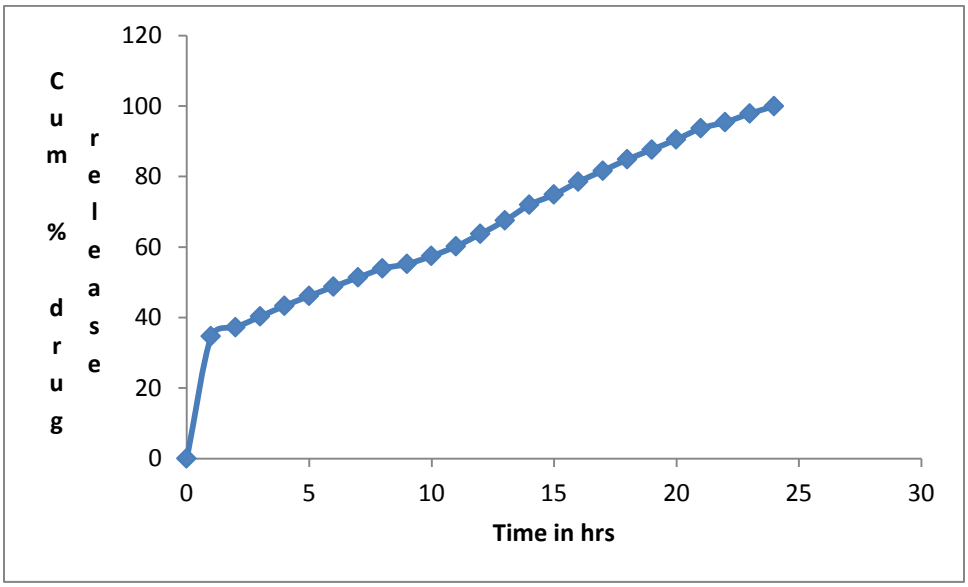


Table:37 Dissolution data of F_8 Formulation at 30°C / 75% RH after 3rd month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	13.51	33.78
2	2	15.29	38.42
3	3	17.35	43.56
4	4	19.27	48.44
5	5	21.13	53.11
6	6	23.43	58.88
7	7	25.30	63.58
8	8	26.87	67.54
9	9	28.57	71.82
10	10	31.24	78.51
11	11	32.44	81.54
12	12	33.28	83.65
13	13	33.79	84.93
14	14	34.15	85.84
15	15	34.92	87.77
16	16	35.58	89.43
17	17	36.0	90.49
18	18	36.41	91.52
19	19	36.72	92.3
20	20	37.02	93.06
21	21	37.80	95.0
22	22	38.13	95.85
23	23	38.32	96.32
24	24	38.52	96.83

Fig:22 Dissolution profile of F_8 Formulation at 30^oC / 75% RH after 3^{rd} month:

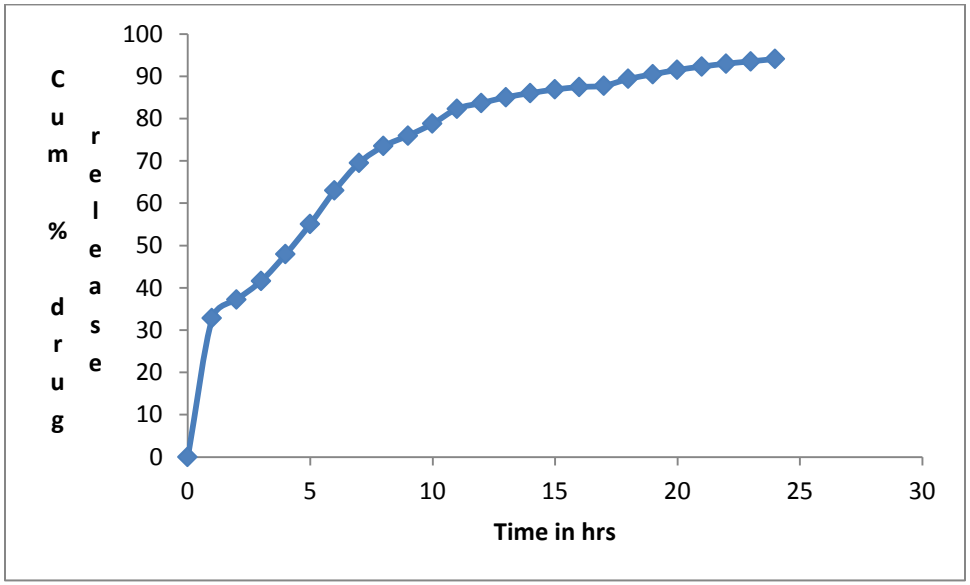
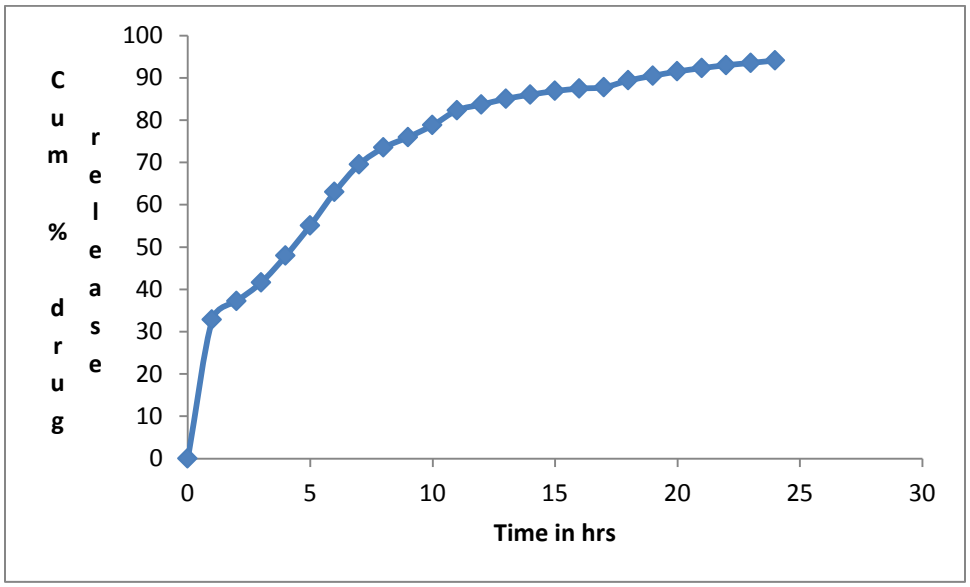


Table:38 Dissolution data of F_8 Formulation at 40°C / 75% RH after 3rd month:

S.No	Time (hrs)	Amount of drug release (mg)	Cummulative % drug release
1	1	13.51	33.78
2	2	15.29	38.42
3	3	17.35	43.56
4	4	19.27	48.44
5	5	21.13	53.11
6	6	23.43	58.88
7	7	25.30	63.58
8	8	26.87	67.54
9	9	28.57	71.82
10	10	29.24	73.50
11	11	30.43	76.48
12	12	31.24	78.51
13	13	32.44	81.54
14	14	33.28	83.65
15	15	33.79	84.93
16	16	34.15	85.84
17	17	34.92	87.77
18	18	35.58	89.43
19	19	36.0	90.49
20	20	36.41	91.52
21	21	36.72	92.3
22	22	37.02	93.06
23	24	37.80	95.0
24	24	38.13	95.85

Fig:23 Dissolution profile of F_8 Formulation at 40^oC / 75% RH after 3^{rd} month:



6.7 PHENOMENON OF DRUG RELEASE:

The formulations were subjected to graphical treatments to access the kinetics of drug release.

Release was approaching Zero order.

Zero order Equation:

The results data was fitted into the Zero order equation.

$Q = K_o t$

Q = The amount of drug release at time t

K_o = Release rate

First order Equation:

The results data was fitted into the First order equation.

$\text{Log } C = \text{Log } C_o - kt / 2.303$

C_o = initial concentration of drug

K = first order constant

t = time

Higuchi Plot:

The graph was plotted between cumulative % release and square root of time. The regression value of F8 was 0.931. This indicates, that **diffusion** is one of the mechanism of drug release.

Peppas Plot:

The graph was plotted between log cumulative % release and log time. The slope (n) value of F8 was 0.978. This indicates, that fickian diffusion mechanism of drug release.

Fig:14 Zero order kinetics Treatment of optimized formulation F8

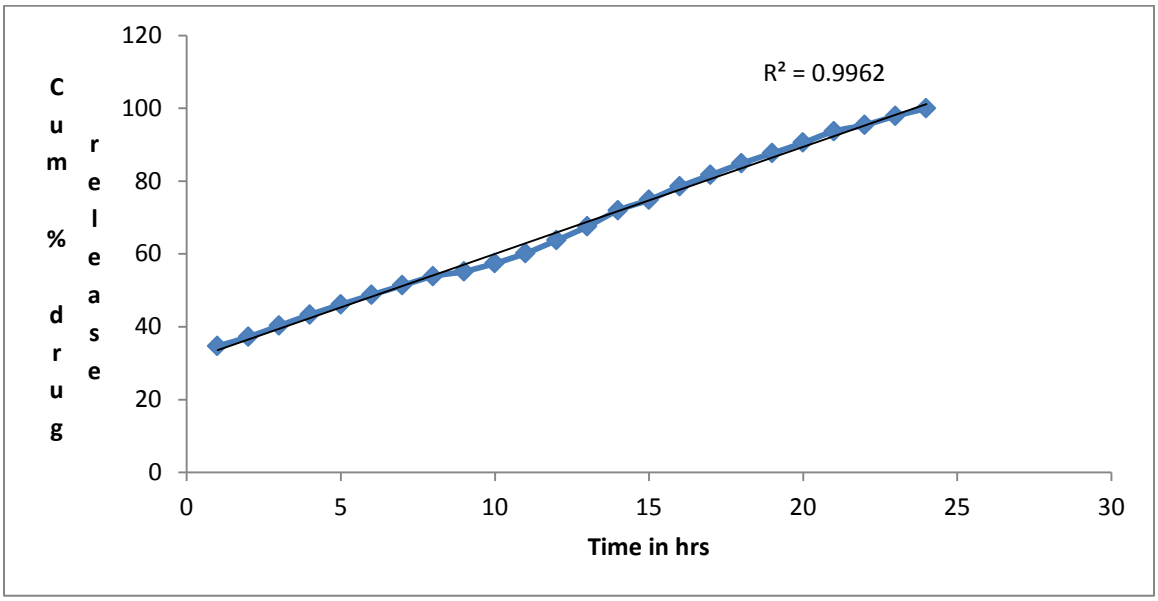


Fig: 15 First order kinetics Treatment of optimized formulation F8

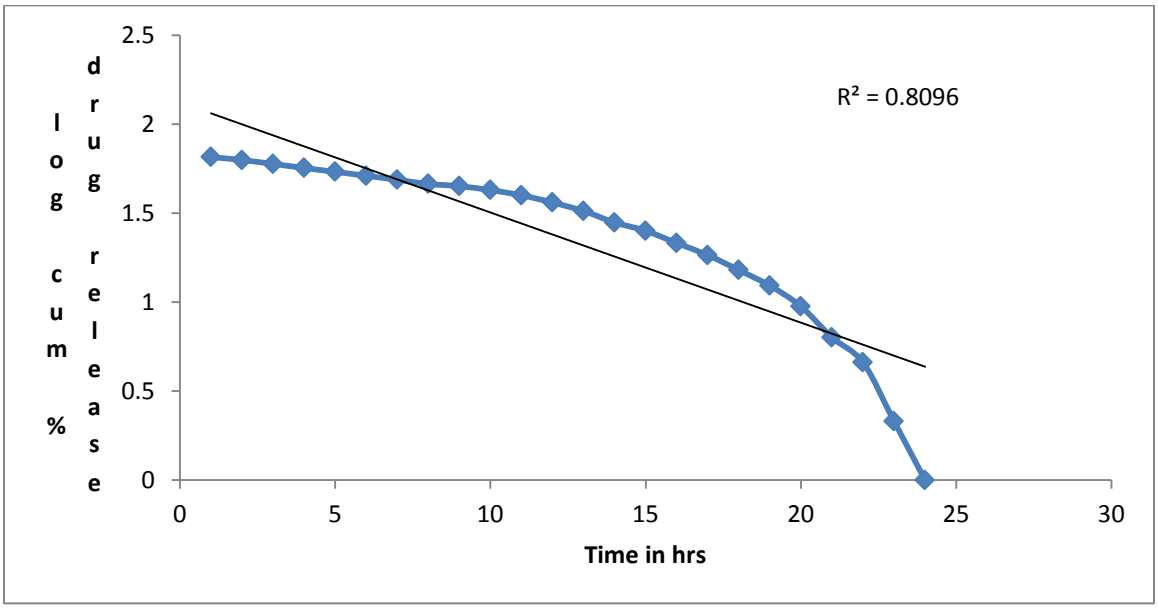


Fig: 16 Higuchi's Treatment of optimized formulation F8

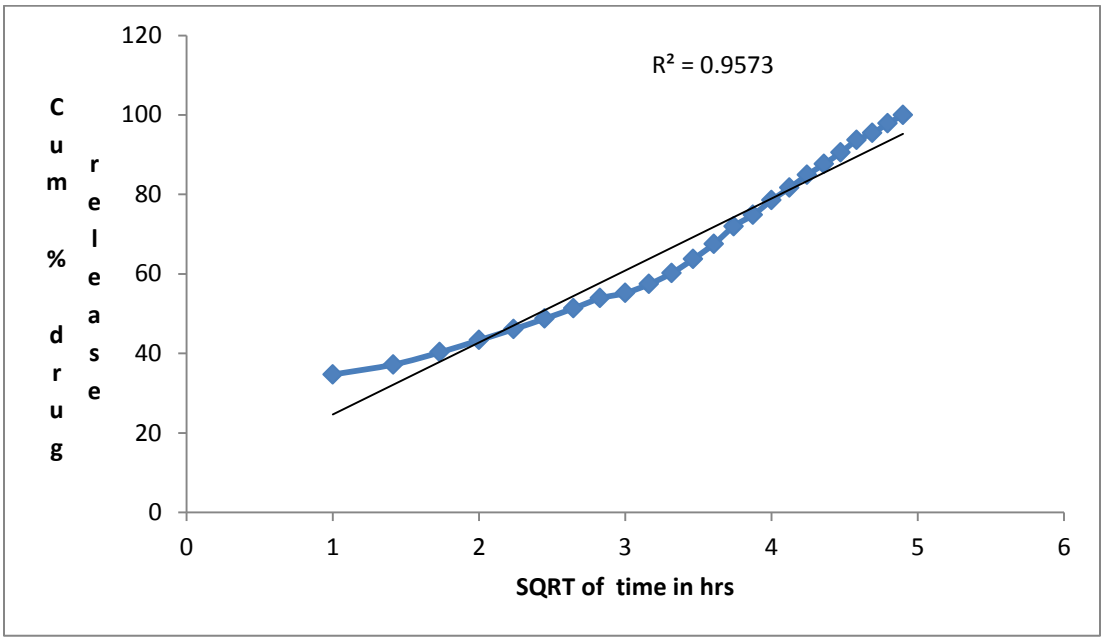
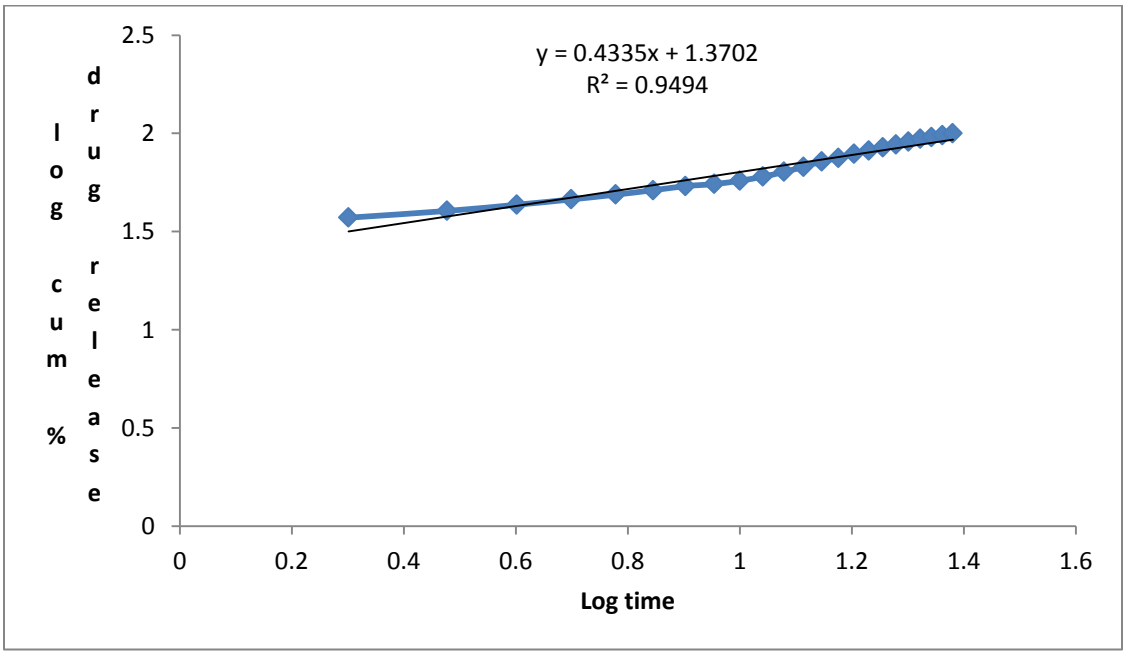


Fig: 17 Peppa's plot Treatment of optimized formulation F8



7. CONCLUSION

The Bilayer tablets of Lurasidone were prepared by direct compression. F_8 is considered to be the optimized formulation with the desired drug release. The polymers which have been used in the best formulation (F8) are Croscarmellose, Crospovidone, HPMC [K4,K100], MCC, starch, sodium lauryl sulphate, Magnesium stearate and Talc.

The granules were evaluated for angle of repose, bulk density, tapped density, hausner's ratio, carr's index and moisture content. The tablets were subjected to weight variation, thickness, hardness, friability, drug content and *in-vitro* release studies.

The results of FTIR analysis of pure drug, drug-excipients mixtures and tablet formulations showed that there was no physical and chemical interaction of drug with the other excipients.

The stability studies of optimized formulation F_8 at 25^oC/60% RH, 30^oC/75% RH, 40^oC/75% RH for 3 months did not show any variation in the tested parameters and release also.

The phenomenon of drug release shown that the release of optimized formulation F_8 is controlled by Fickian diffusion.

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